EXHIBIT C

Article

An algorithm (decision tree) for the management of Parkinson's disease (2001):

Treatment Guidelines

C. Warren Olanow, MD, FRCPC; Ray L. Watts, MD; and William C. Koller, MD, PhD

INTRODUCTION

Parkinson's disease (PD) is named in honor of James Parkinson, whose classic monograph, "An Essay on the Shaking Palsy," written in 1817, has provided an enduring description of the clinical features of this disorder.[1] PD is an age-related neurodegenerative disorder with an average age at onset of 60 years. An estimated 1 million persons in the United States suffer from PD,[2] and there are approximately 60,000 new cases each year. United States Census Bureau projections indicate that there will be a substantial increase in the number of at-risk individuals 60 years of age and older, and therefore the prevalence of PD is likely to increase in the coming decades.

The introduction of levodopa in the late 1960s represented a major therapeutic advance in the management of PD,[3] providing clinical benefit to virtually all patients and reduced mortality. However, it soon became apparent that long-term treatment with levodopa is complicated by the development of adverse events that include motor fluctuations, dyskinesias, and neuropsychiatric complications.[4-6] In addition, with disease progression, patients develop features that do not respond well to levodopa therapy, such as freezing episodes, autonomic dysfunction, falling, and dementia. As a consequence, despite levodopa treatment, most PD patients eventually suffer disabilities that cannot be satisfactorily controlled with existing medical therapies. Therefore, there has been an intensive effort to develop new treatments that reverse disabilities in patients with advanced disease, that provide enhanced clinical benefits with a reduced risk for adverse events, and that slow the rate of disease progression. This has led to an explosion of new laboratory and clinical information and to a variety of new treatment strategies for the management of PD. Physicians who treat PD patients must now assimilate a considerable body of data to optimally manage patients with this complex disorder.

In 1994[7] and 1998,[2] groups of movement disorder experts gathered together to publish an algorithm (decision tree) for the management of PD, with the intent of providing treatment guidelines for the practicing physician. They reviewed the decision-making processes involved in management of PD patients, identifying alternative treatment strategies and areas of controversy when appropriate. Even though it has been a relatively short time since the most recent of these publications, so much new information relevant to the treatment of PD has become available that we feel it is timely to publish an updated algorithm that incorporates this material. From the laboratory perspective, there have been advances in understanding how nerve cells die, the pathophysiology of the basal ganglia in PD, and the molecular basis of levodopa-related motor complications. Gene mutations have been identified in some patients with young-onset and familial PD, and major epidemiologic studies suggest that environmental factors play a dominant role in most cases of sporadic PD. Clinically, there is new information with respect to emerging neuroprotective strategies, the role of dopamine agonists in managing early PD as a way to prevent motor complications, the use of catechol-*O*-methyl transferase (COMT) inhibitors, surgical therapies, and the importance of sleep disturbances in PD, to name just a few. These developments have expanded our treatment options and improved our ability to treat the PD patient in the different stages of the disorder.

We have revised the previous algorithm (decision tree) published in March 1998 as a supplement to *Neurology*[2] to take into account this new information. The format of the previous supplement has been maintained, and it continues to include decision

From the Department of Neurology, Mount Sinai School of Medicine, New York, NY (Dr. Olanow), the Department of Neurology, Emory University School of Medicine, Atlanta, GA (Dr. Watts), and the Department of Neurology, University of Miami School of Medicine, Miami, FL (Dr. Koller).

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Address correspondence to C. Warren Olanow, MD, FRCPC, Department of Neurology, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, Annenberg 1494, Box 1137, New York, NY 10029. Tel: 212-241-8435; Fax: 212-967-7635; E-mail: warren.olanow@mssm.edu

trees for management of the different aspects of PD, the advantages and disadvantages of the various therapeutic agents, and detailed breakouts of selected subtopics. Clinical controversies, as before, are highlighted. Where the guidelines put forward in the 1998 algorithm remain applicable, they were not changed. Where new information is available, particularly from prospective, double-blind, controlled clinical trials, it has been incorporated into the algorithm and the guidelines modified accordingly. This decision tree is designed to aid the physician in identifying and selecting treatment options for patients in the various stages of PD. It is recognized that the treatment of PD is highly individual and that the physician often must employ his or her best judgment. There may often be alternative approaches that are equally valid, and an effort has been made to point these out and to provide data that will help in making treatment choices for the individual patient. Therefore, this decision tree is not meant to represent a singular way to treat PD but rather to serve as a guideline that points out the advantages and disadvantages of the different treatment options. It is our hope that this publication will be of use to clinicians, managed care organizations, and other healthcare providers as they struggle with the difficult and complex decisions involved in caring for the patient with PD.

DIAGNOSIS

The diagnosis of PD may be difficult in the early stages.[8,9] Historically, PD has been diagnosed based on the presence of two of three cardinal features: tremor, rigidity, and bradykinesia. However, diagnosis based on these criteria alone led to an incorrect diagnosis in 25% of cases that had postmortem studies performed at the London Brain Bank.[10] MRI studies similarly indicate that approximately 25% of patients who present with parkinsonism do not have idiopathic PD.[11] It is now evident that many patients who were initially considered to have PD later evolved into a clinical picture more typical of an atypical parkinsonism, such as multiple system atrophy (MSA) or progressive supranuclear palsy (PSP).[12] Retrospective analyses have shown that the clinical features that best predict the pathologic changes of idiopathic PD are resting tremor, asymmetry with one side more affected than the other, and a good response to levodopa.[13] In contrast, the clinical features that best predict atypical parkinsonism are early onset of prominent speech dysfunction and postural instability, axial greater than appendicular rigidity, autonomic dysfunction, dysphagia, and a poor response to levodopa.[14]

The presence of prominent and symptomatic orthostatic hypotension or concomitant cerebellar signs should raise the possibility of MSA. PSP is characterized by an impairment in vertical eye movements, particularly down-gaze.[15] Slowing of vertical saccades or the presence of a prominent stare with marked reduction in blink rate may antecede paralysis of down-gaze and should raise suspicion that the patient might have PSP. Clinical features of atypical parkinsonism in the presence of asymmetric focal rigidity and cortical features such as myoclonus, apraxias, or alien limb phenomenon should raise the possibility of corticobasal ganglionic degeneration (CBD).[16] Even these criteria may not be sufficient to permit an accurate diagnosis in the early stages of these disorders when parkinsonian features are mild and not readily distinguishable.

Some clinicians have used a "levodopa challenge test" in attempts to differentiate PD from atypical parkinsonism. This is not particularly helpful because PD patients with very mild features may not show great benefit from levodopa, and patients with atypical parkinsonism may show some benefit, particularly in the early stages of the disease. Furthermore, animal studies suggest that even a single dose of levodopa may prime the basal ganglia for the subsequent development of dyskinesia[17] (see section on Motor Complications of Levodopa). On the basis of these factors, a consensus panel of PD experts has recommended against using this procedure as a diagnostic test.[18] Drug-induced parkinsonism secondary to neuroleptic agents should be considered if patients are receiving these medications. It is important to recall that neuroleptic agents capable of inducing a parkinsonian syndrome may be used to treat emesis [e.g., prochlorperazine (Compazine), promethazine (Phenergan)] and gastrointestinal (GI) disorders [e.g., metoclopramide (Reglan)]. Other causes of secondary parkinsonism include infarcts and tumors in the basal ganglia, hydrocephalus, and infections such as human immunodeficiency virus (HIV). These should be considered in the differential diagnosis but are usually relatively easy to separate from PD on the basis of other clinical and laboratory criteria. Montgomery et al.[19,20] have developed a diagnostic test battery that distinguishes patients with mild PD from normal control subjects based on a score combining indices of motor performance, olfaction, and depression.

Genetic testing may become more important in the diagnosis of PD. Familial forms of PD with an autosomal dominant pattern of inheritance have been reported in association with mutations in the gene encoding for the proteins α-synuclein and ubiquitin carboxy-terminal hydrolase-L1 (UCH-L1).[21,22] An autosomal recessive form of parkinsonism also has been reported with mutations in the gene encoding for the protein termed parkin.[23-25] These patients tend to have a relatively young-onset parkinsonism with early dystonia, symmetric involvement, a good response to levodopa, levodopa-induced dyskinesias, relatively preserved cognition, and absence of Lewy bodies on postmortem examination. The detection of gene defects either directly associated with the development of parkinsonism or acting as genetic susceptibility factors[26-28] may provide an opportunity for detecting at-risk individuals.

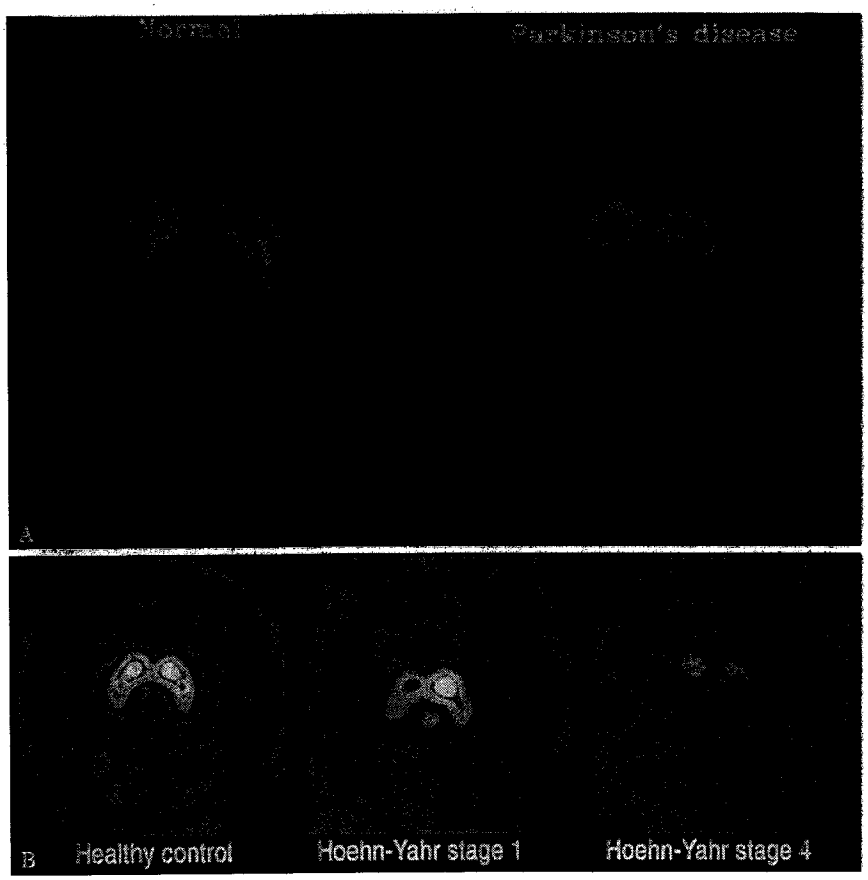


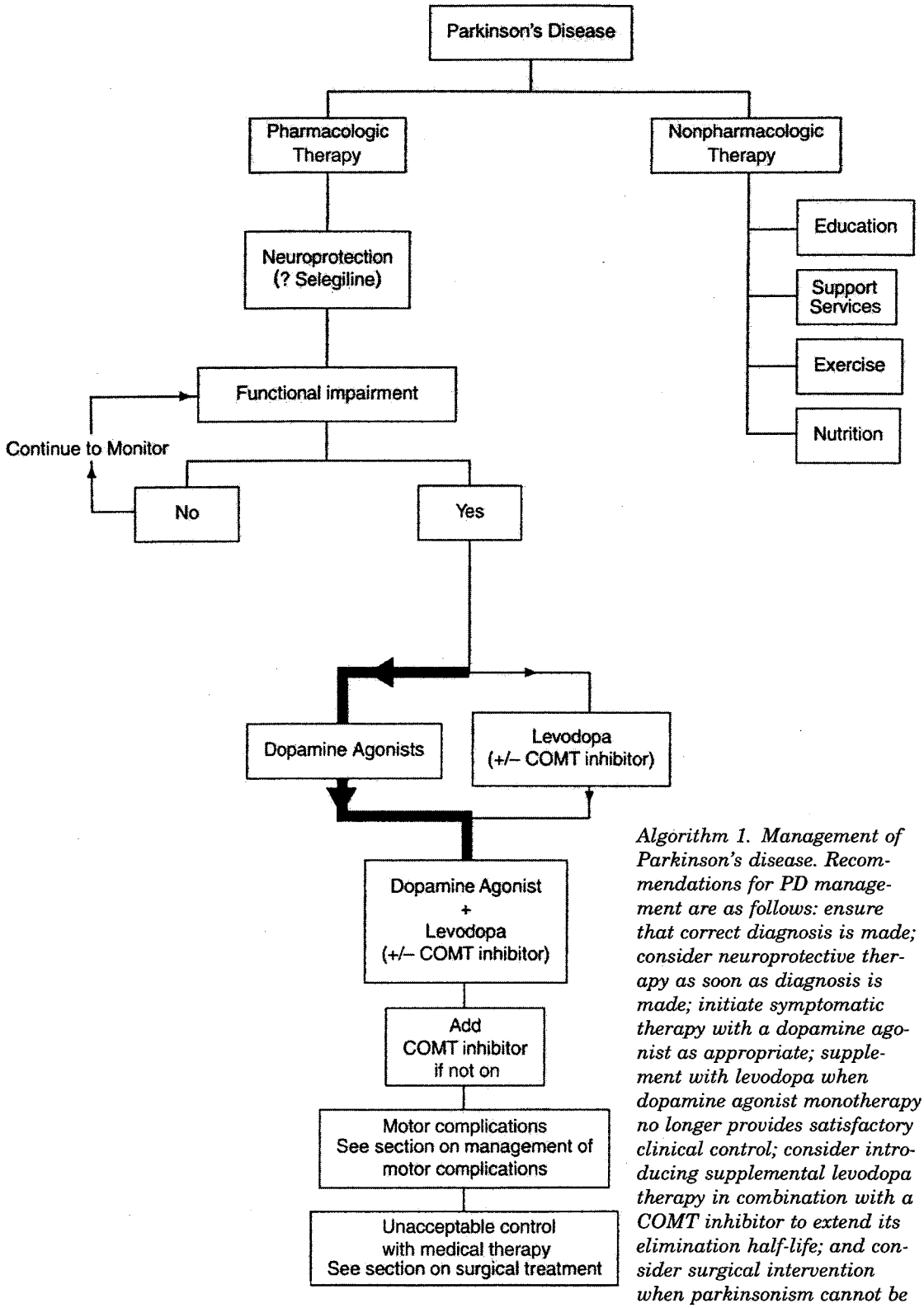
Figure 1. (A) FD-PET scans demonstrate diminished uptake in the brain, particularly in the posterior putamen in PD patients compared with normal controls. (B) β-CIT-SPECT scans demonstrate diminished uptake in the posterior putamen which decreases with the severity of PD. (Courtesy of K.L. Marek.)

Neuroimaging techniques also can be useful in diagnosis, although this is not required in patients with straightforward PD.[11] However, imaging techniques can be valuable in identifying at-risk individuals.[29-36] Specifically, positron emission tomography (PET) and single photon emission computerized tomography (SPECT) can be used to assess the integrity of the nigrostriatal system and metabolic activity within the basal ganglia. Striatal [^{18}F]-fluorodopa (FD) uptake on PET reflects presynaptic dopa decarboxylase activity and is an indirect index of the number of striatal dopamine terminals and nigral neurons.[30-32] Positron-emitting ligands that bind to the dopamine transporter, such as β-carbomethoxy-3-β-(4-iodophenyl) tropane (β-CIT),[33] and to the vesicular monoamine transporter (VMAT), such as [^{11}C]-dihydrotetrabenazine (DTBZ),[35] can also be used to provide an estimate of the number of dopamine terminals and nigral neurons. Striatal FD uptake on PET and β-CIT uptake on SPECT are significantly reduced in PD patients compared with controls, especially in the posterior portion of the putamen (figure 1).[30,31,33,36] The severity of change in striatal FD uptake on PET is closely correlated with clinical deficits and the number of dopaminergic nigral neurons in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys[37] and PD patients.[38,39] Neuroimaging techniques also may be useful in distinguishing PD from atypical parkinsonisms. In the latter, striatal uptake of dopaminergic markers tends to be equally decreased in both the putamen and caudate nucleus, in contrast to the preferential involvement of the posterior putamen in PD.[30] In addition, PET imaging of the postsynaptic D_2 receptor, using ligands such as raclopride, tends to be normal in PD but is slightly reduced in atypical parkinsonisms, reflecting the involvement of postsynaptic structures in these conditions.[30] Eidelberg et al.[34] have developed a methodology for diagnosing PD and separating it from atypical parkinsonism by using fluorodeoxyglucose (FDG)-PET to measure different patterns of metabolic activity within the basal ganglia network. While these neuroimaging techniques are valuable, they are expensive and not widely available for routine clinical use.

PHARMACOLOGIC MANAGEMENT OF PD

Neuroprotection. Neuroprotection in PD can be defined as an intervention that protects or rescues vulnerable nigral neurons and slows or stops disease progression. As soon as a diagnosis of PD has been made, it is appropriate to consider the introduction of a neuroprotective therapy (algorithm 1). Indeed, if a therapy could be established to slow or prevent disease progression, it would reinforce the need to define at-risk patients so that such a disease-modifying therapy could be initiated before the development of clinical dysfunction (see section on Diagnosis).

Neuroprotective therapies can be directed at etiologic or pathogenetic factors or at the cell death pro



Algorithm 1. Management of Parkinson's disease. Recommendations for PD management are as follows: ensure that correct diagnosis is made; consider neuroprotective therapy as soon as diagnosis is made; initiate symptomatic therapy with a dopamine agonist as appropriate; supplement with levodopa when dopamine agonist monotherapy no longer provides satisfactory clinical control; consider introducing supplemental levodopa therapy in combination with a COMT inhibitor to extend its elimination half-life; and consider surgical intervention when parkinsonism cannot be satisfactorily controlled with medical therapies.

cess itself.[40] Ideally, it would be best to identify and eliminate a specific etiologic agent. However, it is likely that many different etiologic factors are capable of causing PD, and multiple factors may contribute to the development of PD in a given individual. Considerable evidence supports a role for both genetic and environmental factors in the etiology of PD. Approximately 5 to 10% of PD patients have a familial pattern of inheritance, suggesting that in these individuals genes play a dominant role.[26,28,41] Many candidate genes have been studied, and linkage has been reported with several.[28,42] Of particular interest is the recent finding in a large Italian PD kindred (the Contursi kindred) and in two smaller and possibly related Greek kindreds of a mutation in the gene on chromosome 4q21-q23 that encodes for the protein α-synuclein.[21] This mutation leads to a substitution of an alanine for a threonine at position 53 (A53T) in the amino acid sequence of the protein. An additional mutation in which an alanine is substituted for a proline at position 30 (A30P) has since been discovered, confirming that these mutations are relevant to the development of PD. These findings demonstrate that a single gene mutation can cause a PD syndrome. Familial PD also has been associated with mutations in the genes that encode for UCH-L1[22] and parkin.[23-25] Although these gene mutations do not appear to account for the vast majority of cases of PD, they provide an opportunity to develop better models of PD, to gain insight into mechanisms responsible for cell death and to test putative neuroprotective therapies. α-Synuclein is a soluble, natively unfolded protein with the capacity to aggregate and form insoluble amyloid fibrils.[43,44] This raises the possibility that critical mutations can cause the protein to misfold, accumulate within the cell, and induce secondary cell damage. The finding that α-synuclein aggregates in Lewy bodies even in patients with sporadic PD[45] suggests that protein accumulation caused by genetic or environmental factors may be a key to the pathogenesis of cell death in PD. Indeed, overexpression of mutant α-synuclein and, to a lesser degree, wild-type α-synuclein can induce degeneration of dopamine neurons in both in vitro and in vivo models,[46,47] suggesting that excessive accumulation of proteins may be a fundamental problem in PD.

A Japanese group of investigators[23-25] has described several different mutations in the gene on the long arm of chromosome 6 that encodes for the protein parkin in patients with an autosomal recessive, young-onset form of PD. Indeed, a European study has identified mutations in the parkin gene in 47% of patients with young-onset parkinsonism.[48] This suggests that genetic screening for the parkin gene in young-onset patients may be useful in detecting at-risk individuals and may permit the early introduction of a potentially neuroprotective therapy. Interestingly, parkin has been determined to be a ubiquitin–protein ligase that is involved in protein degradation, and mutant forms of parkin lose this activity.[49] It therefore appears that all the gene defects thus far identified in PD are associated with factors related to protein structure and/or clearance. This raises the possibility that impaired clearance of proteins due to genetically or environmentally mediated alterations in their structure or in the degradation process may be a common event underlying all cases of PD. Substantiation of this concept will provide novel opportunities for developing neuroprotective therapies.

Whereas gene defects have been implicated in patients with young-onset PD, a major epidemiologic study suggests that genetic factors do not play a role in patients with PD beginning after the age of 50 years, a group that comprises the bulk of PD patients.[50] This study utilized the World War II United States Veteran Twin Registry maintained by the National Academy of Science to assess concordance of PD in monozygotic and dizygotic twins. For patients with PD beginning under the age of 50 years, concordance for PD was significantly greater in monozygotic than in dizygotic twins, consistent with the notion that genes play a major role in these patients. However, for PD patients with onset over the age of 50 years, the concordance rate was no different in the two groups, suggesting that environmental factors are more important in cases of sporadic PD. Epidemiologic studies demonstrate an increased risk for development of PD in association with exposure to rural living, well water, pesticides, herbicides, and wood pulp mills.[51,52] A PD-like syndrome has also been described in association with the toxin MPTP[53] and with infectious agents.[54] In addition, a recent study demonstrated that chronic administration of the selective complex I inhibitor rotenone can injure nigral dopaminergic neurons and induce a PD-like syndrome in rodents.[55] Epidemiologic studies to further evaluate the potential role of rotenone are warranted because it is a widely employed pesticide. Interestingly, there appears to be an inverse relationship between the risk for development of PD and use of coffee, caffeine, or smoking,[56,57] although how these might exert a possible beneficial effect on PD is unknown.

It is likely that a pure genetic or environmental cause accounts for only a small number of PD patients. In the majority, it is more likely that PD results from a complex interaction among multiple genes and proteins that may be different in different individuals. One possibility is the so-called "double-hit hypothesis," which suggests that patients develop PD if they carry a susceptibility gene *and* have exposure to a particular toxin. This hypothesis suggests that a gene defect and exposure to an environmental toxin are both necessary to induce clinical PD.

Factors that have been implicated in the pathogenesis of PD include oxidative stress, excitotoxicity, mitochondrial dysfunction, and inflammation (see review by Olanow et al.[58]). Interference with one or more of these factors might block the pathogenetic cascade involved in the neurodegenerative process

and thus provide neuroprotective benefits. There is also increasing information suggesting that cell death in PD occurs via an apoptotic mechanism.[59,60] Apoptosis is a relatively gradual form of cell death that is characterized morphologically by fragmentation of DNA with relative absence of inflammation. It was initially described in relation to the death of excess numbers of developing neurons, but apoptosis is now known to occur in response to a number of PD-related toxins and in a variety of neurodegenerative diseases, including PD.[40,61] Increasing evidence indicates that apoptosis probably develops in response to mitochondrial signals that either initiate the degenerative process or inhibit normal protective mechanisms.[61] Nigral neurons may be at particular risk for apoptosis because they are routinely exposed to radical species derived from the oxidative metabolism of dopamine.[62] Moreover, in PD this propensity may be increased by the reduction in oxidative defenses and the underlying mitochondrial defects that have been described in nigral neurons.[62,63] This represents an opportunity to introduce anti-apoptotic therapies that interfere with intracellular signals that promote the development of neurodegeneration, regardless of the specific etiology or pathogenesis.

It is also possible that the natural history of PD can be altered by trophic factors that rescue damaged dopaminergic neurons or by transplantation strategies that replace dopaminergic cells or precursors. Evidence reviewed above suggesting that neurodegeneration in PD may result from the pathologic accumulation and/or aggregation of proteins provides additional targets for neuroprotective therapies. It is therefore evident that there are many different opportunities for providing neuroprotective or rescue effects in PD. These are summarized in table 1.

Clinically, some physicians use the selective MAO-B inhibitor selegiline (Deprenyl, Eldepryl) as a putative neuroprotective therapy. Selegiline was approved for use in PD as an adjunct to levodopa because it modestly increases the percent of "on" time in advanced PD patients (see section on Motor Complications of Levodopa). However, selegiline has been used in clinical practice primarily as a possible neuroprotective agent based on its capacity to inhibit the MAO-B oxidation of MPTP to the toxin MPP^+ and thereby to prevent dopaminergic toxicity induced by this toxin.[64,65] It has further been postulated that selegiline might slow the rate of neuronal degeneration in PD by blocking the formation of free radicals derived from the oxidative metabolism of dopamine.[62] In previously untreated PD patients, prospective, double-blind, controlled clinical trials (DATATOP[66,67] and SINDEPAR[68] studies) have demonstrated that selegiline delays the emergence of disability and the progression of motor signs and symptoms in comparison with placebo[66-69] (figure 2).[67] These findings are consistent with a neuroprotective effect of the drug. However, post-hoc analyses have shown that selegiline can induce symptomatic effects that might account for some or all of these benefits.[70]

Table 1 *Possible mechanisms for obtaining neuroprotection*

Antioxidant agents
Free radical scavengers (vitamin E, glutathione, spin-trap agents)
Glutathione
Iron chelators
Agents that block glutamate-mediated toxicity
Excitatory amino acid antagonists
Glutamate-release inhibitors (e.g., Riluzole)
Glutamate reuptake enhancers
Nitric oxide synthesis inhibitors
Poly (ADP-ribose) polymerase inhibitors
Calcium channel blockers
Mitochondrial bioenergetics
Creatine
Co-enzyme Q10
Ginkgo biloba
Nicotinamide
Carnitine
Anti-inflammatory agents
Nonsteroidal anti-inflammatory agents (e.g., COX-2 inhibitors)
Steroids
Estrogens
Trophic factors
GDNF
Immunophillins
Transplant strategies
Human fetal nigral transplantation
Porcine fetal nigral transplantation
Anti-apoptotic agents
Desmethylselegiline, TCH-346
Caspase inhibitors
Agents that maintain closure of mitochondrial pore (e.g., cyclosporine)
Agents that prevent protein accumulation and aggregation

Although there remains a question as to whether or not selegiline provides neuroprotective effects in PD patients, the drug has clearly been shown to have neuroprotective effects in a variety of in vitro and in vivo laboratory models.[71] Furthermore, selegiline provides neuroprotective effects in these models through a mechanism that does not depend on MAO-B inhibition[72-75] and derives from its metabolite desmethylselegiline (DMS).[76,77] Selegiline neuroprotection is now believed to be due to an anti-apoptotic mechanism that involves upregulation of antioxidant and anti-apoptotic molecules such as glutathione, superoxide dismutase (SOD), and BCL-2.[77-79] Tatton and colleagues[80] have demonstrated that DMS and other propargylamines act by binding to the protein glyceraldehyde-phosphate dehydrogenase (GAPDH) and preventing its accumulation in the nucleus, where

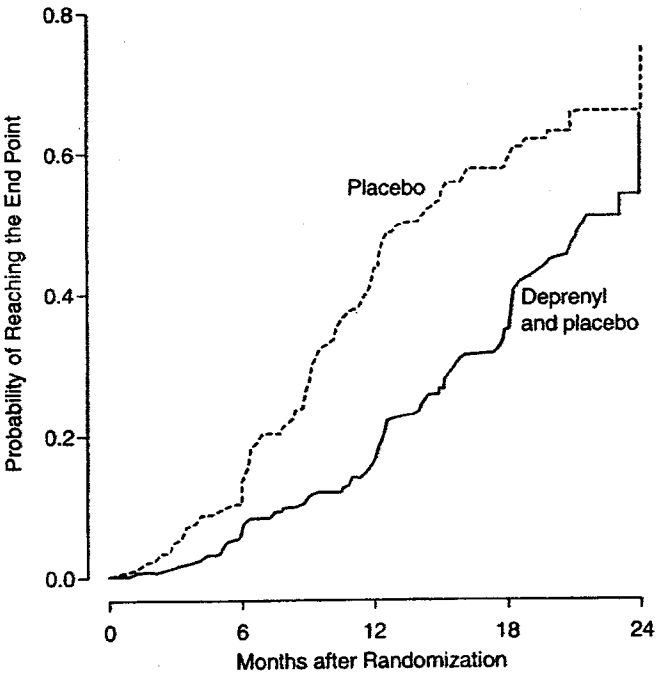


Figure 2. Kaplan-Meier curves demonstrating that patients assigned to placebo had a greater probability of reaching the end point (need for levodopa) than patients randomized to Deprenyl. (Adapted with permission from the Parkinson Study Group.[67])

it exerts pro-apoptotic effects. GAPDH normally has a tetrameric configuration. Under conditions of mitochondrial stress, GAPDH is released from its RNA binding site and accumulates in the nucleus, where it blocks transcriptionally mediated increases in the anti-apoptotic protein BCL-2, thereby promoting apoptosis. Propargylamines such as DMS bind to a central channel in the GAPDH molecule and maintain it as a dimer, in which form it does not translocate to the nucleus or promote apoptosis. Another propargylamine, TCH-346, which does not inhibit MAO-B and does not have amphetamine metabolites, has particularly pronounced anti-apoptotic properties in both in vitro and in vivo models,[81,82] and this agent is now being tested as a possible neuroprotective agent in PD.

It is not now possible to state conclusively that selegiline has a neuroprotective effect in PD. It clearly does not halt disease progression,[83] and in some studies initial benefits have not been maintained.[84,85] The Parkinson Disease Research Group of the United Kingdom[86] reported increased mortality in PD patients who initiated therapy with selegiline plus levodopa compared to levodopa alone. However, this study has been criticized for methodological and statistical flaws,[87] and increased mortality in selegiline-treated patients has not been observed in any other trial.[88]

Selegiline is administered at a dose of 5 mg twice daily and is generally well tolerated as monotherapy. When selegiline is combined with levodopa, it can enhance dopaminergic side effects and lead to increased dyskinesia and neuropsychiatric problems,

***Therapeutic Breakout 1** Selegiline*

Advantages
As adjunct to levodopa, provides reduced motor fluctuations and increased "on" time
Levodopa-sparing effect
Neuroprotective in laboratory models
May be neuroprotective in PD
Disadvantages
Minimal antiparkinsonian effect
Neuroprotection in PD not established
Does not stop disease progression
Has amphetamine and methamphetamine metabolites

particularly in the elderly. Some physicians use lower doses (e.g., 5 mg or less per day) in an attempt to avoid these problems. Amphetamine metabolites of selegiline may induce insomnia, and for this reason the drug is usually not prescribed to be taken after noon. The advantages and disadvantages of selegiline are illustrated in therapeutic breakout 1.

Rasagiline is another MAO-B inhibitor that is now being evaluated in PD. Like selegiline, it is a propargyl derivative that can provide protective effects in both in vitro and in vivo model systems.[89] It does not generate amphetamine metabolites but has not been demonstrated to have additional advantages over selegiline, and has not been shown to provide protective effects in PD patients.

Vitamin E (α-tocopherol) in doses of 2,000 IU was tested as a neuroprotective agent in PD as part of the DATATOP study.[67] No delay in disease progression was detected.[67] Therefore, there is no basis at present for recommending vitamin E to PD patients as a neuroprotective therapy. Dopamine agonists are now being tested in several clinical trials as putative neuroprotective agents on the basis of their capacity to induce (a) a levodopa-sparing effect, (b) activation of dopamine autoreceptors with decreased dopamine synthesis, release, and metabolism, (c) direct antioxidant effects, (d) receptor-mediated anti-apoptotic effects, and (e) inhibition of excitotoxicity mediated by overactivity of the subthalamic nucleus (STN).[90-93] Multicenter trials also are testing the potential of riluzole (a sodium channel blocker that inhibits glutamate release) and co-enzyme Q10 (a bioenergetic that acts as a co-factor for complex I and as an antioxidant) to provide neuroprotective effects in PD. Both have been shown to provide protective benefits for dopaminergic neurons in PD models.[94-96]

Neuroimmunophillins, which bind to a part of the cyclosporine receptor, have been shown to protect and rescue dopaminergic neurons in 6-hydroxydopamine (6-OHDA)-treated rodents.[97] The neuroimmunophillin AMGEN-474 is now being tested in PD patients as a putative neuroprotective agent. Glial-derived neurotrophic factor (GDNF) has been shown to restore dopaminergic function in the MPTP-treated monkey,[98] but preliminary clinical trials in PD patients were nega-

tive. This may be because GDNF was delivered into the ventricle and did not enter the brain parenchyma. Further trials with direct intraparenchymal implantation are anticipated. Double-blind controlled trials of human and porcine fetal nigral transplantation have been initiated in an attempt to restore nigrostriatal dopaminergic activity. The first study using human fetal nigral cells failed to meet its primary outcome, a quality of life measure (see section on Surgical Management). However, benefits were detected in more traditional outcomes of motor function, and the results of further studies are awaited. In addition to all of the above, there remains great interest in the potential of surgical manipulation of overactive glutamate-producing brain target sites such as the subthalamic nucleus, gene therapies, and stem cells to provide neuroprotective or rescue effects for PD patients (see section on Future Directions).

The list of agents that might provide neuroprotective effects in PD is daunting, and we are left with the challenge of determining how we will find the resources (patients and funds) to study so many promising therapeutic opportunities[99] (see table 1). It will also be necessary to define an outcome variable for measuring disease progression that is acceptable to clinicians and regulatory authorities. The DATATOP study[66,67] used the time to reach a disease milestone (i.e., need for levodopa) as the primary end point. However, interpretation of results was confounded by the drug's symptomatic effect. The SINDEPAR study[68] used change in motor score between initial and final visits performed after patients had been washed out of all study medications as the primary end point. However, antiparkinsonian medications have now been shown to have a long duration response that can last for at least 2 weeks after drug withdrawal.[100] It is therefore difficult to be certain that all symptomatic effects have been eliminated. Modern studies utilize FD-PET and β-CIT-SPECT as surrogate markers for the number of remaining nigral neurons. Both techniques demonstrate an approximate 5–10% annual decline in striatal uptake in patients with early PD,[36,101,102] suggesting that neurodegeneration is an ongoing process in these patients. It remains, however, to confirm that decreased striatal uptake of isotope with these methods does in fact correlate with degeneration of nigrostriatal neurons and that there is no confounding pharmacologic effect. To date, no drug has been approved for a neuroprotective indication, and regulatory agencies have not yet confirmed that any of the outcome measures described above are acceptable for drug approval. It will probably be necessary to provide evidence of improvement in both imaging and clinical markers of disease progression before it can be declared that an intervention has a neuroprotective or disease-modifying effect.

Symptomatic therapy

When to initiate symptomatic therapy. The decision about when to initiate symptomatic treatment for PD is somewhat controversial. Some advocate early treatment to provide patients with maximal clinical benefit at the start of their illness.[103-105] Others prefer to delay initiation of treatment to minimize the risk for development of long-term motor complications and/or acceleration of disease progression consequent to oxidative radicals derived from levodopa metabolism.[106-111] Most movement disorder specialists start treatment when a patient begins to experience functional impairment. In the DATATOP study, the time point for initiating symptomatic therapy was when a patient experienced impairment in managing activities of daily living, had threatened loss of employability, or developed gait disturbance with a risk for falling.[112] The definition of functional impairment, however, must be considered on an individual basis because patients progress at different rates[113] and parkinsonian features may have different functional implications for different individuals. Factors that influence the determination of whether a patient has functional impairment include the following:

1. whether symptoms affect the dominant or nondominant hand,
2. whether the patient is employed or employable and how parkinsonian features affect ability to work,
3. parkinsonian features that are present (e.g., bradykinesia tends to be more disabling than tremor), and
4. patient and physician treatment philosophy.

Although these issues may appear straightforward, the decision to treat is often not easily reached, and assessing the impact of parkinsonian features on an individual patient may be difficult. If no symptoms were present, obviously the patient would not have sought medical attention. Therefore, the issue is not whether there is impairment but, rather, whether there is functional impairment that represents a source of disability to the patient. In most early PD patients, symptoms are predominantly unilateral, and the degree of functional impairment often depends on which hand is affected. A patient with dominant-hand involvement will have more functional impairment than a patient with the same degree of impairment of the nondominant hand. Parkinsonian patients with symptoms of gait impairment or postural instability should be considered to have functional impairment even if they themselves deny it, because these problems can lead to falls and serious injury. Employment is an important consideration. All things being equal, the same degree of dysfunction is more likely to cause disability in a patient who is working because even minor symptoms can impair job performance and threaten employability.

An important determinant of functional disability is the degree to which symptoms interfere with motor function and activities of daily living. The Unified Parkinson's Disease Rating Scale (UPDRS)[114] is a

useful way to maintain an ongoing record of patient function and to assess disability. The Activities of Daily Living (ADL) component of the UPDRS evaluates speech, salivation, swallowing, handwriting, cutting food, handling utensils, hygiene, turning in bed, falling, freezing, walking, tremor, and sensory symptoms. Careful questioning, using the ADL scale as a framework, can provide insight into the degree of patient disability and provides a means of monitoring the evolution of parkinsonism over time. Copies of the UPDRS form can be obtained from We Move at 204 West 84th St., 3rd Floor, New York, NY 10024, or it can be downloaded from its website at www.wemove.org.

Drug therapies

Levodopa. Levodopa is the most effective drug in the treatment of PD. Treatment is associated with decreased morbidity and mortality in comparison to the pre-levodopa era,[104] and virtually all patients with pathologically confirmed PD experience clinically meaningful benefit.[13] Levodopa is routinely administered in combination with a decarboxylase inhibitor to prevent the peripheral conversion of levodopa to dopamine and the resultant nausea and vomiting that can occur due to stimulation of dopamine receptors in the area postrema that are not protected by the blood–brain barrier. In the United States, the decarboxylase inhibitor carbidopa is combined with levodopa and marketed as Sinemet. Dosage strengths of 10/100, 25/100, and 25/250 are available, with the first number representing the dose of carbidopa and the second number the dose of levodopa. In Europe, the decarboxylase inhibitor benserazide is combined with levodopa and is sold under the trade name of Madopar. It is available in doses of 25/100 and 50/200, as well as in a 25/100 water-dispersible tablet. Controlled-release formulations of Sinemet (Sinemet CR) in doses of 25/100 and 50/200 and Madopar (Madopar HBS) in doses of 50/200 are also available. Liquid preparations of levodopa (made from regular formulations of levodopa on an individual basis) provide more rapid absorption and can be used in an attempt to control complex patients who are extremely sensitive to even minor changes in levodopa dosage.[115] Methyl ester and ethyl ester water-soluble formulations of levodopa are rapidly absorbed and are now under investigation for use in PD. They can be administered subcutaneously to induce a rapid response in patients experiencing a severe "off" state or orally for those with delayed "on" episodes.[116,117] Parenteral forms of levodopa are also potentially valuable in the management of PD patients who undergo surgery and cannot take medications orally.

In general, it is better to start with low doses of levodopa and increase the dose gradually to minimize the risk for acute side effects, such as nausea, vomiting, and hypotension. Patients are titrated to a clinically effective dose over weeks or months. If more rapid effects are desired, Sinemet 25/100 can be initiated at a three times daily (tid) dose, but there is a greater risk that they will have side effects. It is generally recommended to employ the lowest dose of levodopa that provides a satisfactory clinical response. In the early stages of the disease, this can usually be accomplished with 300 to 400 mg per day administered in divided doses. Controlled-release formulations of levodopa are less well absorbed than regular formulations, and doses 20 to 30% higher may have to be administered to achieve the same clinical effect. It is usually best to administer levodopa when the patient has an empty stomach, to facilitate absorption and avoid competition with dietary proteins (see section on Nutrition), even though many pharmacists label for levodopa to be taken with meals. A practical approach is to dose 1 hour before or after eating. Parkinsonian patients who fail to respond to high doses of levodopa (>1,000 mg) probably have an atypical parkinsonism rather than PD and are unlikely to respond to other dopaminergic drugs.[118]

It is estimated that decarboxylase inhibitors such as carbidopa must be employed at a dose of at least 75 mg per day to fully inhibit decarboxylase activity. If a patient is receiving a small dose of Sinemet or Madopar, it may not contain a sufficient amount of the decarboxylase inhibitor, and in some individuals it may be necessary to provide additional carbidopa to adequately inhibit the decarboxylase enzyme. If a patient continues to experience nausea or vomiting with clinically effective doses of Sinemet, supplemental carbidopa (Lodosyn) at doses up to 300 mg per day can be prescribed. Supplemental carbidopa can usually be discontinued when higher doses of Sinemet are employed or after the patient has developed tolerance to the adverse event. The peripheral dopamine receptor antagonist domperidone, at doses of 10 to 20 mg administered 30 minutes before each levodopa dose, can be effective in preventing these side effects. Unfortunately, domperidone is not currently available in the United States. Trimethobenzamide hydrochloride (Tigan 200 mg tid) can be used instead but is not usually as effective. With the use of these strategies (extra carbidopa or addition of an antiemetic), it is very rare for a PD patient to be unable to tolerate levodopa because of acute side effects. However, if orthostatic hypotension is prominent and does not attenuate over time or respond to carbidopa or domperidone, the possibility that the patient might suffer from MSA rather than PD should be considered.

Chronic levodopa is associated with a series of motor complications that include dyskinesia and motor fluctuations (table 2). PD patients can also experience fluctuations in nonmotor symptoms, such as mood, cognition, autonomic disturbances, pain, and sensory function.[119] Neuropsychiatric problems, such as cognitive impairment, confusion, and psychosis, can all be a part of the PD spectrum and can be aggravated by levodopa and by other antiparkinsonian agents. In addition, new features may develop

Table 2 Motor complications of levodopa therapy

Motor fluctuations
End of dose ("wearing off")
Unpredictable motor fluctuations ("on-off" phenomenon)
Dose failures
Freezing episodes
Dyskinesia
Peak-dose dyskinesia
Diphasic dyskinesia; D–I–D
Dystonia

with disease progression that do not respond to levodopa. These include freezing episodes, postural instability with falling, autonomic dysfunction, mood disturbances, and dementia. A fuller discussion of these problems and their management is provided in the appropriate sections that follow.

Levodopa toxicity. There has been a theoretical concern that levodopa treatment might promote neuronal degeneration in PD because of this agent's potential to generate free radicals by way of its oxidative metabolism[62,109,111,120,121] (figure 3).[2] In the laboratory, levodopa has been shown to be toxic to cultured dopaminergic neurons.[122,123] However, the concentration of levodopa employed may be substantially higher than that present in the striatum of levodopa-treated PD patients. Furthermore, cultured dopamine neurons may lack defense mechanisms that are present in the intact brain. Levodopa increased neuronal damage to animals pretreated with MPTP or 6-OHDA in some studies[124,125] but not in another, in which levodopa actually promoted recovery of nigral neurons in 6-OHDA-treated rodents.[126] Administration of large doses of levodopa to normal rodents and humans has not been shown to damage dopaminergic neurons.[127,128] Still, this may not be the case in PD, where the substantia nigra pars compacta (SNc) is in a state of oxidant stress and defense mechanisms are compromised.[121]

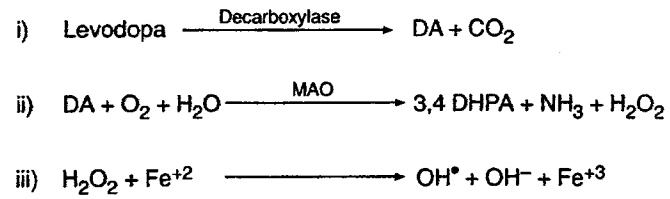


Figure 3. Equations illustrating how levodopa can be converted to dopamine and lead to the formation of oxidizing species and cytotoxic free radicals. (i) Levodopa is decarboxylated to form dopamine (DA). (ii) Dopamine is oxidized by monoamine oxidase (MAO) to yield hydrogen peroxide (H_2O_2). (iii) Under normal circumstances, H_2O_2 is detoxified by glutathione (not shown). However, H_2O_2 has the potential to react with ferrous iron and generate the highly reactive and cytotoxic hydroxyl ($OH^•$) radical according to the Fenton reaction. In addition, both levodopa and dopamine can undergo spontaneous autooxidation to yield reactive oxygen species. Data from Olanow.[62] (Reproduced with permission from Olanow and Koller.[2])

Levodopa did not accelerate the progression of parkinsonian signs and symptoms in comparison to a dopamine agonist in one clinical trial[68] and has not prevented the robust survival of transplanted fetal nigral neurons in PD patients.[129] A consensus conference on the topic of levodopa toxicity concluded that there is at present no evidence to indicate that levodopa is toxic to nigral neurons in PD patients.[130] While the possibility that levodopa might be toxic in PD cannot be excluded, it was recommended that levodopa use not be restricted for this reason alone. A National Institute of Health (NIH)-funded, prospective, double-blind clinical trial (the ELLDOPA study) has been designed to test the effect of different doses of levodopa versus placebo on disease progression and will hopefully resolve this important question.

Motor Complications of Levodopa. Although levodopa provides antiparkinsonian benefit throughout the entire course of PD, chronic levodopa treatment is associated with adverse events that limit its utility.[4-6,131-133] Motor complications can be divided into two subgroups, motor fluctuations and dyskinesia. The various subgroups of motor complications are illustrated in table 2.

Motor fluctuations consist of alterations between periods of relatively good mobility and motor function or "on" periods in which the patient responds to medication, and periods of impaired motor function or "off" responses in which the patient does not respond to medication or the response is suboptimal.[133] During the early stages of PD the clinical response following a single levodopa dose is stable and long lasting (>4 hours) despite the drug having a relatively short plasma half-life of approximately 60 to 90 minutes.[134] Indeed, benefits are frequently maintained even if a dose is missed (the "long-duration response"). With advancing PD, patients begin to experience a wearing-off effect in which the motor benefit after a dose of levodopa is reduced in duration and lasts less than 4 hours (the "short-duration response"). Over time, the duration of benefit after a single dose of levodopa progressively shortens and approximates the plasma half-life of the drug, even though levodopa plasma pharmacokinetics remain unchanged throughout the course of the disease.[135-137] Eventually, patients may begin to experience rapid and unpredictable fluctuations between "on" and "off" periods, known as the "on–off" phenomenon.

As described above, PD patients experience both a short- and a long-duration response to levodopa. The benefit associated with the short-duration response to levodopa typically develops, plateaus, and abates over several hours after dose administration. The duration of the motor response is a function of disease severity, becoming progressively shorter with advancing disease.[136-138] The latency from the time of levodopa administration to the onset of motor im-

provement is typically about 30 to 90 minutes with the standard formulation or 60 to 180 minutes with the controlled-release formulation. Patients with delayed gastric emptying may experience a delay in achieving a motor response because levodopa is absorbed exclusively in the small intestine. To tailor therapy for an individual patient, the clinician should be aware of the magnitude and duration of the motor response after a dose of levodopa/carbidopa as well as the relationship between "on" and "off" periods and dyskinesias. This can sometimes be determined from the patient history but may require prolonged observation with monitoring of several dosing cycles.

The "long-duration response" is the time from complete withdrawal of levodopa until parkinsonian deterioration is maximal (usually 1 to 2 weeks).[99] It is now believed that the long-duration response is an important component of motor fluctuations,[135] because the long-duration response determines the baseline function on which "on" and "off" fluctuations occur. However, the long-duration response is difficult to assess in a routine clinical setting because it involves taking patients off medication for a sustained period of time. This must be done with caution because it may be associated with severe worsening of parkinsonism and the development of a neuroleptic, malignant-like syndrome.

Levodopa-induced dyskinesias are involuntary movements that occur in response to levodopa administration. Movements are typically choreiform or dance-like in character but may involve dystonia, myoclonus, or other movement disorders. They have been viewed as a disruption of the ability of the basal ganglia to facilitate the automatic selection and execution of motor tasks.[139] Virtually any part of the body may be involved, including the head, neck, torso, limbs, and respiratory muscles. Other drugs, such as anticholinergics, also can induce dyskinesia,[140] but these typically involve oro–facial–lingual muscles, as occurs in tardive dyskinesia. When dyskinesia manifests itself as dystonia, it tends to involve the distal extremities. Dystonia is often the earliest manifestation of levodopa-induced dyskinesia and is usually followed by more classic choreiform movements. Dystonia can occur as a feature of untreated PD and also can occur in both "on" and "off" states in response to increased or decreased levodopa doses. It is therefore important to distinguish whether dystonia occurs in "off" periods and is a function of too little levodopa or in "on" periods and is a function of too much levodopa. Advanced patients may experience diphasic dyskinesia or the dyskinesia–improvement–dyskinesia (D–I–D) syndrome,[141] in which they exhibit dyskinesia as they begin to turn "on" and again as they begin to turn "off" but are free of dyskinesia at the time of the peak levodopa effect.

Levodopa-induced dyskinesias tend to develop in conjunction with the development of motor fluctuations. They are reversible and disappear with the reduction or elimination of levodopa. However, a reduction in the levodopa dose is usually associated with deterioration in parkinsonism. Most PD patients prefer to be "on" with dyskinesia rather than "off," but in some patients the dyskinesia can be more disabling than the parkinsonism, particularly when respiratory muscles are involved.

When patients first begin to experience motor complications, they have a relatively wide "therapeutic window," and it is usually possible to find a dose of levodopa that controls parkinsonian features and that does not induce dyskinesia. Unfortunately, with advancing disease, this therapeutic window narrows and it becomes increasingly difficult to find a dose of levodopa that both is effective and does not cause dyskinesia. Therefore, patients may cycle between "on" periods that are complicated by dyskinesia and "off" periods in which they are akinetic and severely parkinsonian. At this stage, levodopa-induced motor complications can be extremely difficult to control and can become a major source of disability. Eventually, it may become impossible to delineate a dose of levodopa that provides motor benefit without inducing dyskinesia.

Motor complications occur in approximately 50 to 90% of PD patients who have received levodopa for 5 to 10 years,[4,6,131,142,143] and constitute a major source of disability. They are a particular problem in patients with young-onset PD, in whom they occur in virtually 100%, and they are less likely to occur in those whose symptoms begin after the age of 70 years.[144-146] They also tend to be seen more frequently in association with high doses of levodopa.[147] In the DATATOP study,[85] 46 to 49% of patients experienced motor fluctuations and 21 to 31% had dyskinesia after a mean duration of levodopa treatment of 20.5 months.[85] The prevalence of motor fluctuations and dyskinesia after 5 years of levodopa treatment in the Sinemet CR First Study was only 20% in patients treated with either regular or controlled-release formulations of levodopa.[148-150] The low frequency observed in this study may have been related to the method by which motor complications were determined and to the relatively low doses of levodopa that were employed. A summary of the prevalence of levodopa motor complications in different studies is provided in table 3.[85,107,147,149-154]

Mechanism of levodopa-induced motor complications. Understanding the mechanisms responsible for the development of levodopa-induced motor complications might help in the design of therapeutic strategies aimed at reducing the risk for their occurrence. Much of our present approach to treating PD and levodopa-induced motor complications derives from the classic model of the basal ganglia.[155,156] This model suggests that the input region of the basal ganglia (the striatum) communicates with the output region [the globus pallidus pars interna (GPi) and the substantia nigra pars reticularis (SNr)] by way of direct and indirect striato–pallidal pathways (figure 4). Neurons in the direct and indirect pathways

Table 3 Studies of the prevalence of levodopa-induced motor complications

Study	Prevalence of complication	Length of study	Method of evaluation
Rajput et al. 1984[107]	10% fluctuations 25% dyskinesias	5 years	Physician evaluation
Poewe et al. 1986[147]	52% wearing off 54% dyskinesias	6 years	Webster Scale Modified Columbia Scale
Hely et al. 1994[151]	41% wearing off 55% dyskinesias	5 years	Modified Columbia Scale Dyskinesia Scale Physician evaluation
Montastruc et al. 1994[152]	40% wearing off 56% dyskinesias	5 years	Columbia Scale UPDRS
Dupont et al. 1996[150]	59% fluctuations 41% dyskinesias	5 years	UPDRS, part 4
Parkinson Study Group. 1996[85] (DATATOP)	50% wearing off 30% dyskinesias	2 years	Physician evaluation UPDRS, part 4
Koller et al. 1999[149] (Sinemet CR First)	20% wearing off 20% dyskinesias	5 years	Patient diary Physician-recorded questionnaire
Rascol et al. 2000[153]	45% dyskinesias	5 years	UPDRS, dyskinesia scale
Parkinson Study Group. 2000[154]	30% dyskinesias	2 years	Physician determination

serve to respectively inhibit or excite basal ganglia output regions and thus influence their effect on the motor thalamus and, ultimately, on the cortical motor regions. Dopamine appears to exert a dual action on striatal neurons, activating D_1 receptors on striatal neurons in the "direct pathway" and inhibiting D_2 receptors on striatal neurons giving rise to the "indirect pathway."[157] These concepts, and their limitations, are extensively reviewed by Obeso et al.[158-160]

The model predicts that parkinsonian motor features and levodopa-induced dyskinesia are, respectively, related to an increase or a decrease in firing frequency of basal ganglia output neurons and the consequent effects of these changes on thalamic and cortical motor areas. With respect to parkinsonism, the model suggests that dopamine depletion leads to increased firing activity in STN excitatory neurons and reduced firing in striatal neurons comprising the direct pathway. These changes combine to result in increased firing of GPi and SNr neurons, with consequent overinhibition of the thalamus, reduced activation of cortical motor regions, and resultant parkinsonian motor features. This concept is supported by neurophysiologic studies demonstrating increased neuronal firing rates in the GPi and STN in PD patients and MPTP-treated monkeys[156,160-162] and has led the way to the development of surgical procedures aimed at reducing neuronal activity in these structures as a treatment for PD[163-167] (see section on Surgical Treatments).

The classic model of the basal ganglia has served us less well when it comes to understanding the origin of levodopa-induced motor complications and, more specifically, levodopa-induced dyskinesia.[159] In support of the model, microelectrode recordings in parkinsonian monkeys and PD patients document a dramatic reduction in GPi firing frequency coupled with the onset of dyskinesia after infusion of the

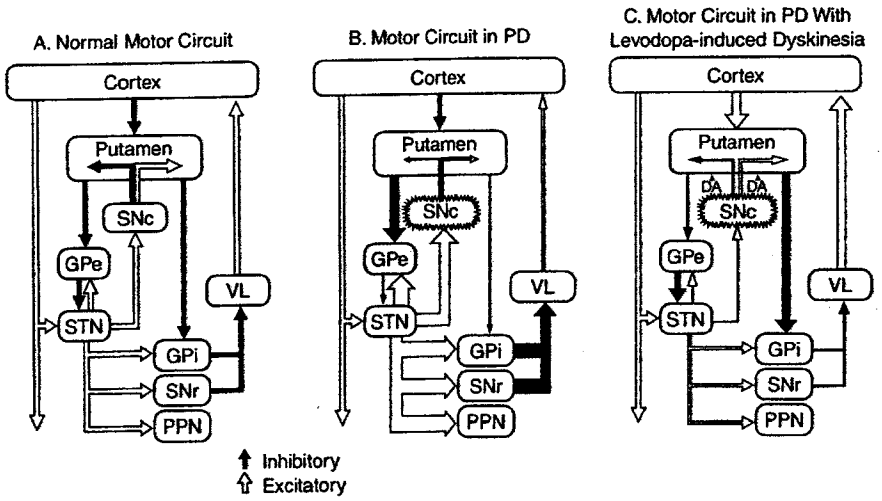


Figure 4. Classic model of the organization of the basal ganglia in the normal (A), parkinsonian (B), and levodopa-induced dyskinetic (C) states. GPe = globus pallidus pars externa; GPi = globus pallidus pars interna; PPN = pedunculopontine nucleus; SNc = substantia nigra pars compacta; SNr = substantia nigra pars reticularis; STN = subthalamic nucleus; VL = ventralis lateralis. STN and GPi are upregulated in the parkinsonian state, leading to increased inhibition of brainstem and thalamocortical neurons with the development of parkinsonian motor features. In contrast, dyskinesia is believed to be related to decreased firing in the STN and GPi, with reduced inhibition of thalamus and motor cortical regions. (Courtesy of C.W. Olanow. Reproduced with permission from Obeso et al.[159])

dopamine agonist apomorphine.[168,169] However, the model does not explain why pallidotomy, which profoundly reduces the neuronal output of the GPi, is consistently associated with amelioration rather than induction of dyskinesia as predicted by the model[163,164] (see section on Surgical Treatments).

A clearer picture of the factors responsible for the origin of motor complications has begun to emerge.[160,170] The duration of the motor response after a levodopa infusion in groups of PD patients with mild, moderate, and severe disease correlates inversely with disease severity despite the fact that all groups have comparable plasma levodopa pharmacokinetics.[137,138] These findings gave rise to the notion that motor fluctuations in patients with advanced PD are associated with a decreased capacity to store levodopa because of the loss of dopaminergic terminals.[171] However, similar findings are obtained after infusion of apomorphine, which is not stored in dopaminergic terminals.[172,173] These findings cannot be explained by the "storage hypothesis." Furthermore, shortening of the duration of the motor response occurs in 6-OHDA-lesioned rodents treated with repeated doses of levodopa[174] even though the lesion is stable and, presumably, the capacity to store levodopa has not changed. These findings support the notion that there is a postsynaptic component to the development of motor complications. It is now becoming apparent that motor complications are related to both presynaptic and postsynaptic events that include abnormal pulsatile stimulation of the dopamine receptor, dysregulation of genes and proteins in downstream neurons, and altered firing patterns in basal ganglia output neurons (see Olanow and Obeso[170] for a more detailed discussion).

Pulsatile stimulation of striatal dopamine receptors appears to be the key to the induction of levodopa-related motor complications. Under normal circumstances, dopamine is released in both a tonic and a phasic manner. Because tonic firing predominates and because the dopamine reuptake system is extremely rapid, there is a relatively constant level of dopamine at the level of the synapse and continuous stimulation of dopamine receptors.[175,176] Two factors contribute to the likelihood that abnormal pulsatile stimulation of the receptor will occur: (a) loss of striatal dopaminergic terminals, with a consequent loss in their ability to store dopamine and regulate its release, and (b) intermittent administration of a dopaminergic agent with a short half-life. In the early stages of PD, there are still adequate numbers of residual dopamine terminals in the brain to store dopamine and buffer fluctuations in plasma levodopa concentration and thus to permit relatively continuous and physiologic stimulation of dopamine receptors. With advancing disease, there is a progressive degeneration of dopaminergic terminals, and brain dopamine levels become dependent on the availability of peripheral levodopa. Therefore, fluctuations in the plasma concentration of levodopa result in fluctuations in brain levodopa/dopamine levels, and dopamine receptors are exposed to alternating high and low concentrations of dopamine.

Considerable evidence supports the notion that pulsatile stimulation of striatal dopamine receptors is responsible for the induction of levodopa motor complications. Levodopa induces shortening of the motor response in parkinsonian rodents when it is given intermittently but not when it is administered continuously.[177] Levodopa and short-acting dopamine agonists are more prone to induce dyskinesia in MPTP-treated monkeys than are long-acting dopaminergic agents.[17,178-180] Indeed, the same short-acting experimental dopamine agonist induces dyskinesia when administered in a pulsatile manner but not when administered continuously.[181] These different patterns of dopamine receptor stimulation presumably elicit different functional responses because they activate different signal transduction pathways that regulate different genes and proteins in postsynaptic neurons.[182] Pulsatile stimulation of dopamine receptors in MPTP-treated monkeys induces upregulation of genes such as preproenkephalin (PPE) and ΔFosB, which correlate with the development of dyskinesia.[183,184] These molecular changes are, in turn, associated with alterations in the firing pattern of basal ganglia output neurons that include changes in the number and duration of firing bursts and pauses, changes in the degree of neuronal synchrony, and changes in neuronal firing rates.[185] In the final analysis, miscoded information is relayed from basal ganglia output neurons to cortical motor regions, resulting in the emergence of dyskinesia and other motor complications. It is the elimination of this abnormal neuronal firing pattern that probably accounts for the antidyskinetic effect of pallidotomy. On the basis of these considerations, it has been hypothesized that therapies that deliver more continuous dopamine receptor stimulation will provide antiparkinsonian effects with a reduced risk for development of motor complications.[186-188] A summary of the advantages and disadvantages of levodopa is provided in therapeutic breakout 2.

Dopamine agonists. Dopamine agonists are a class of drugs with diverse physical and chemical properties which share the capacity to directly stimulate dopamine receptors, presumably because they incorporate a dopamine-like moiety within their molecular configuration.[118] There has been considerable interest in this class of drugs because of their potential to provide antiparkinsonian effects while avoiding some of the problems associated with levodopa. Historically, they have been used primarily as adjuncts to levodopa in patients who have begun to experience motor complications. A growing body of laboratory and clinical data now suggests that it is preferable to employ dopamine agonists as initial symptomatic therapy to reduce the risk for development of the motor complications associated with levodopa therapy. Until recently, however, there has been little clinical information supporting the early use of dopamine agonists, and no controlled clinical

***Therapeutic Breakout 2** Levodopa*

Advantages
Most symptomatically efficacious antiparkinsonian drug
Virtually all PD patients respond
Improves disability and prolongs capacity to maintain employment and independent activities of daily living
May improve mortality rate
Disadvantages
Majority develop adverse events
Dyskinesia: choreiform movements, dystonia
Motor fluctuations
Neuropsychiatric problems: confusion, psychosis
Sedation
Does not treat all features of PD, such as freezing, postural instability, autonomic dysfunction, and dementia
Does not stop disease progression
Theoretically, oxidative metabolites may accelerate disease progression

trials have compared them to levodopa with respect to the risk for inducing motor complications.

In the United States, bromocriptine (Parlodel) and pergolide (Permax) have been used in the treatment of PD for many years. Three new dopamine agonists have been introduced to the market for the treatment of PD: pramipexole (Mirapex), ropinirole (Requip), and cabergoline (Cabsar, Dostinex). As a group they have been more extensively studied than the older dopamine agonists in the early stages of PD. Cabergoline has not been promoted for the treatment of PD in the United States, but it is marketed for this indication in some European countries and in Japan. The dopamine agonists lisuride, piribedil, and apomorphine also are available in some countries outside of the United States. Table 4 provides information about the usual starting doses and therapeutic dose ranges for each of these agents.

Dopamine agonists offer several theoretical advantages over levodopa.[118,189-193] First, dopamine agonists act directly on dopamine receptors and do not require metabolic conversion to an active product in order to exert their pharmacologic effect. They therefore act independently of the degenerating dopaminergic neurons. In addition, they have the potential to directly stimulate subsets of dopamine receptors, in theory providing an opportunity to obtain benefits with reduced incidence of adverse events. Second, in contrast to levodopa, circulating plasma amino acids do not compete with dopamine agonists for absorption and transport into the brain.[194] Third, marketed dopamine agonists have a longer half-life than immediate-release and controlled-release formulations of levodopa, and individual doses therefore have the potential to provide more sustained stimulation of striatal dopamine receptors. Finally, they do not undergo oxidative metabolism and do not generate free radicals or induce oxidative stress. Indeed, there is mounting evidence suggesting that they may have neuroprotective effects.[90]

***Table 4** Dopamine agonist dose ranges**

Drug	Initiating dose (mg)	Usual dose range (mg/day)
Bromocriptine	1.25 bid–tid	7.5 –40
Pergolide	0.05 qd	0.75 –6
Pramipexole	0.125 tid	0.75 –3
Ropinirole	0.25 tid	9 –24
Cabergoline	0.25 qd	0.5 –5
Lisuride	0.2 qd	1 –2

* Dopamine agonists should be introduced at a low dose and gradually titrated to optimal clinical benefit over the course of several weeks to months.

The newly approved dopamine agonists ropinirole and pramipexole differ from the older agonists in that they are non-ergot derivatives and are relatively selective in stimulating dopamine D_2 and D_3 receptors. Ropinirole does not stimulate α- and β-adrenergic receptors, γ-aminobutyric acid (GABA), 5-HT_1, or 5-HT_2 receptors,[195] whereas pramipexole does stimulate α_1- and α_2-adrenergic receptors but not serotonin receptors. This contrasts with bromocriptine and pergolide, both of which stimulate a wider array of nondopaminergic receptors. In clinical practice, the role played by the different receptors in normal motor function or in motor complications remains unclear.

Dopamine agonists have long been known to be efficacious in PD, having been employed since the 1970s as adjuncts to levodopa for patients with advanced PD who experience motor complications.[118,193] Bromocriptine was the first dopamine agonist to be approved as a treatment for PD. It is an ergot derivative that is a D_2 receptor agonist and a weak D_1 receptor antagonist. Several studies have demonstrated the capacity of bromocriptine, used as an adjunct to levodopa, to improve parkinsonian disability and reduce dyskinesia and motor fluctuations in patients with advanced PD.[196-198] Pergolide is also an ergot agent with D_2 receptor agonist properties, but it differs from bromocriptine in that it is a weak agonist of the D_1 receptor. A large, prospective, multicenter, double-blind, placebo-controlled trial in levodopa-treated patients demonstrated that pergolide improved motor and ADL scores, decreased "off" time, and provided a levodopa-sparing effect (figure 5).[199] Similar results have been obtained with lisuride and cabergoline when these agents were used as adjuncts to levodopa.[200,201]

Placebo-controlled studies have also demonstrated that pramipexole and ropinirole exert antiparkinsonian and levodopa-sparing effects in levodopa-treated PD patients.[202-205] In a 6-month, double-blind, controlled study, 49% of levodopa-treated PD patients randomized to ropinirole achieved a 20% or greater reduction in levodopa dose compared with only 17% of placebo controls ($p<0.001$).[204] This bene-

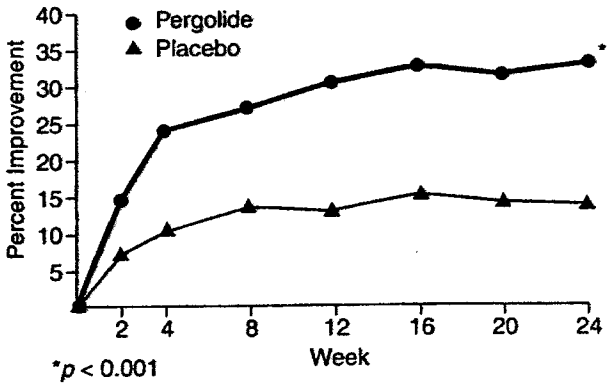


Figure 5. Percent improvement in total Parkinson score (sum of motor and activities of daily living disability score) by treatment group in a 24-week, double-blind, placebo-controlled study. At week 24, the total Parkinson score was significantly greater with pergolide compared to placebo. (Reproduced with permission from Olanow et al.[199])

fit was associated with a reduction in daily "off" time of 3.7 hours in the ropinirole group compared to 1.6 hours in the placebo group. Similarly, in a 32-week, placebo-controlled, double-blind study, pramipexole improved motor function (25% versus 12%; $p<0.001$), decreased time spent in "off" (31% versus 7%; $p<0.001$), and reduced the dose of levodopa (27% versus 5%; $p<0.001$).[202] In these studies, ropinirole was initiated at a dose of 0.25 mg tid and gradually increased to a total of 3–24 mg per day based on clinical response. Pramipexole was initiated at a dose of 0.125 mg tid and titrated up to a maximal dose of 4.5 mg per day.

Apomorphine has been used as a "rescue agent" for patients with advanced PD who suffer severe "off" periods. Administered parenterally, it provides rapid but short-lasting benefit,[206,207] but it can be useful in the acute management of unpredictable "off" episodes. Apomorphine is usually administered subcutaneously but can also be administered by intramuscular, sublingual, rectal, oral, and transdermal routes. Although apomorphine can be very helpful for some patients, it is difficult to manage and is frequently associated with nodules and ulcerations at sites of administration. Furthermore, domperidone or another agent that can block emesis must be co-administered with apomorphine, at least initially. At present, apomorphine is not available in the United States.

Dopamine agonists have also been used with limited success in treating patients with complex motor fluctuations and severe dyskinesia. One approach is the use of high doses of dopamine agonists as a substitute for levodopa. In one study, pergolide at doses of up to 13 mg per day permitted a 90% reduction in levodopa dose and was associated with improvement in dyskinesia and parkinsonian disability.[208] Unfortunately, this approach is associated with potentially serious side effects and has limited applicability for most PD patients. Another approach is administration of dopamine agonists in a continuous fashion.[209] Although the responsible mechanism has not been defined, continuous administration of a dopamine agonist (either around the clock or throughout the waking day) has been consistently reported to reduce "off" time but to either improve or worsen dyskinesia.[210-212] These studies have all been open-label, and psychiatric complications have been a major problem.[213] This approach also requires considerable time and effort on the part of the patient, family, physician, and nurse. Therefore, continuous dopaminergic stimulation paradigms are likely to be of limited use in routine practice, but they do provide some insight into the nature of dyskinesias.

Despite the benefits provided by the adjunctive use of dopamine agonists, levodopa-related motor complications can be extremely difficult or even impossible to control (see section on Management of Motor Complications). In fact, motor complications that are refractory to medical treatment are in large part responsible for the resurgence of interest in surgical therapies for PD. Accordingly, there has been considerable interest in the development of treatment strategies that prevent their occurrence. There is mounting evidence supporting the use of dopamine agonists as initial symptomatic therapy for PD. This is based on the growing body of laboratory evidence indicating that they can protect against the pulsatile stimulation of striatal dopamine receptors that is associated with the development of motor complications (see above).[158,159,170-172,177-181,186,188,214] As noted above, Bédard et al.[178] were the first to demonstrate that long-acting dopamine agonists such as bromocriptine are associated with a markedly reduced incidence of dyskinesia in MPTP monkeys compared to levodopa. Although both groups experienced comparable motor benefits, dyskinesia developed in 10/10 levodopa-treated animals, whereas dyskinesia occurred in only 1/14 animals that received bromocriptine. In MPTP-treated marmosets, Pearce et al.[179] similarly showed that bromocriptine and ropinirole were associated with a significant reduction in the frequency and severity of dyskinesia compared to levodopa, despite the fact that each treatment provided comparable motor benefits (figure 6).[188] It is likely that the decreased incidence of motor complications observed with dopamine agonists is related to their relatively long half-lives rather than to their specific molecular structure, because short-acting dopamine agonists such as quinpirole or CY-208 can rapidly induce dyskinesia, much like levodopa.[215,216] Furthermore, the same short-acting agonist induces dyskinesia when given intermittently but not when administered continuously.[181] It is noteworthy that, in the MPTP-treated monkey, long-acting dopamine agonists, such as ropinirole or bromocriptine, or short-acting dopamine agonists administered continuously prevent the upregulation of PPE and the appearance of dyskinesia that occurs with levodopa treatment or intermittent administration of a short-acting dopamine agonist.[181,184] These observations

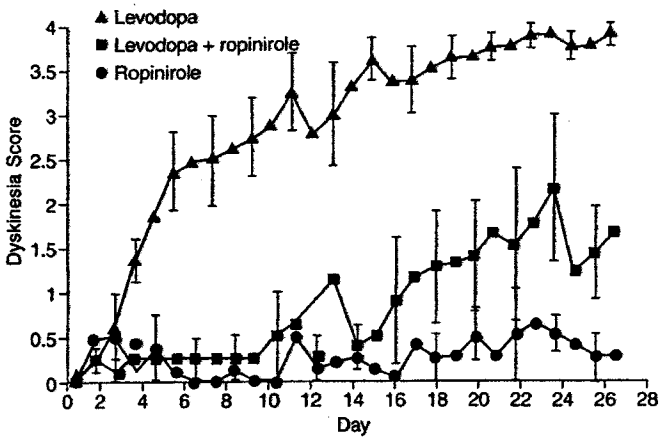


Figure 6. Frequency of dyskinesias in MPTP-treated marmosets treated with levodopa, levodopa plus ropinirole, or ropinirole alone (n = 4 per group). Levodopa treatment is associated with increased frequency and severity of dyskinesia in comparison with the dopamine agonist ropinirole. Administration of levodopa in combination with ropinirole is associated with less dyskinesia than levodopa alone, but the frequency and severity are greater than in animals treated with ropinirole alone. (Courtesy of P. Jenner. Reproduced with permission from Olanow et al.[188])

are consistent with the concept that long-acting dopamine agonists prevent dyskinesia by avoiding levodopa-induced postsynaptic changes that occur secondary to pulsatile stimulation of the dopamine receptor. Interestingly, there is some evidence to suggest that, in MPTP-treated monkeys, exposure to even a single dose of levodopa primes for the development of dyskinesia.[17,216] Indeed, while dopamine agonists such as ropinirole and bromocriptine do not induce dyskinesia when administered to previously untreated parkinsonian animals, they do induce dyskinesia if the animal has been previously exposed to levodopa.

These observations have fueled interest in the notion that it may be better to initiate symptomatic therapy in PD with a relatively long-acting dopamine agonist rather than with a relatively short-acting formulation of levodopa (table 5). A series of open-label clinical studies support this claim, with most,[151,152,217,218] but not all,[219] showing that the early use of a dopamine agonist is associated with fewer motor complications than with levodopa. However, until recently dopamine agonists have not been studied in the early stages of the disease with well-designed prospective, double-blind, controlled clinical trials. Studies now have been performed in early PD patients comparing dopamine agonists to placebo and to levodopa with respect to both symptomatic effects and the risk for development of motor complications.

Prospective double-blind, controlled studies clearly demonstrate the superiority over placebo of pramipexole, ropinirole, and pergolide[220-223] (figure 7). Only a few studies have directly compared dopamine agonists to levodopa as monotherapy in otherwise untreated PD patients. A prospective single-blind, double-observer

***Table 5** Half-life of dopaminergic agents*

Drug	$t_{1/2}$ (h)
Cabergoline	24
Carbidopa/levodopa	1–1.5
Pergolide	7–16
Pramipexole	8–12
Ropinirole	6–8

study demonstrated that bromocriptine was comparable to levodopa during the first 6 months of treatment but was inferior thereafter.[218] More recently, a 6-month double-blind study demonstrated that patients randomized to receive treatment with ropinirole had clinical benefits that were only slightly inferior to those randomized to levodopa (44% versus 32% improvement).[224] Indeed, benefits were comparable to levodopa for patients in the early stages (Hoehn and Yahr stages I and II) of the disease (figure 8).[2,224] In addition, approximately 50% of PD patients can be satisfactorily controlled with dopamine agonist monotherapy for 3 years and more than 30% can remain on dopamine agonist monotherapy for 5 years before requiring levodopa supplementation[153,224] (figure 9).

Of greater importance are studies addressing the frequency of motor complications in patients randomized to initiation of therapy with a dopamine agonist versus levodopa. Prospective double-blind, multicenter studies have now been performed comparing initial treatment with ropinirole,[153] pramipexole,[154] or cabergoline[225] to levodopa. Similar studies have been undertaken with pergolide but have not yet been reported. The primary outcome measure for the ropinirole study was the incidence of dyskinesias, whereas the pramipexole and cabergoline studies used a composite outcome measure consisting of the time to development of any motor complication (dyskinesias, wearing-off effects, or "on–off" fluctuations). These studies all demonstrate that the motor complications associated with levodopa therapy are significantly reduced in patients randomized to initiation of therapy with a dopamine agonist.

The first of these studies to be reported was the 5-year double-blind trial comparing ropinirole to levodopa in 268 untreated PD patients.[153] Patients with early PD (average duration 2.5 years) who required dopaminergic treatment were randomized to begin therapy with either ropinirole or levodopa plus a decarboxylase inhibitor. Ropinirole was initiated at a dose level of 0.25 mg tid and levodopa at a dose level of 50 mg tid. The blinded "dose level" could be increased at weekly intervals until satisfactory control was achieved or side effects developed. The maximal daily doses of medication that could be prescribed by increasing the blinded dosing level of the study medication were 24 mg of ropinirole and 1,200 mg of levodopa. If the investigator deemed PD

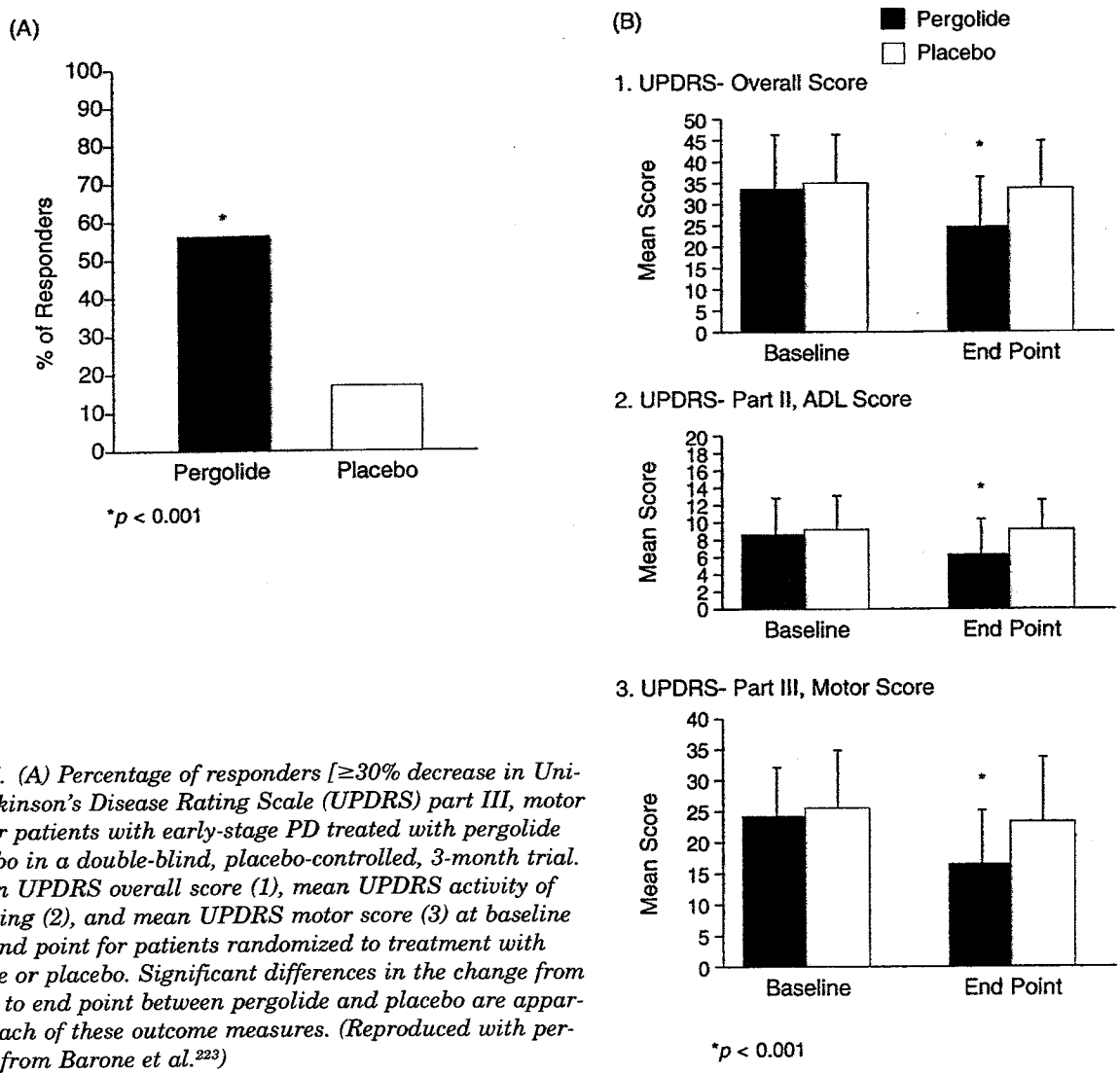
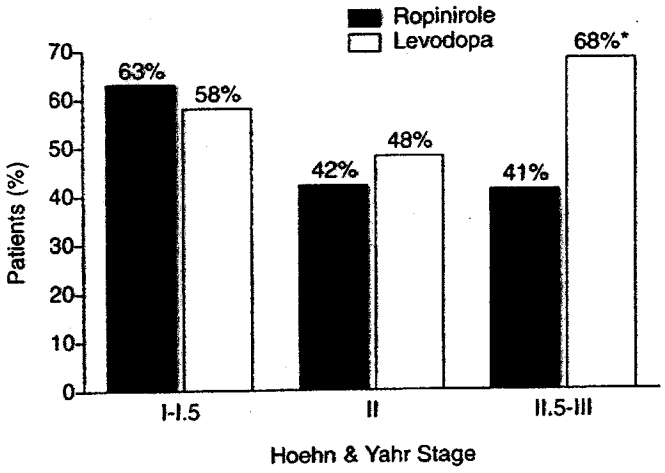


Figure 7. (A) Percentage of responders [≥30% decrease in Unified Parkinson's Disease Rating Scale (UPDRS) part III, motor score] for patients with early-stage PD treated with pergolide or placebo in a double-blind, placebo-controlled, 3-month trial. (B) Mean UPDRS overall score (1), mean UPDRS activity of daily living (2), and mean UPDRS motor score (3) at baseline and at end point for patients randomized to treatment with pergolide or placebo. Significant differences in the change from baseline to end point between pergolide and placebo are apparent for each of these outcome measures. (Reproduced with permission from Barone et al.[223])

features to be inadequately controlled by adjustment of the blinded study medication, supplementary open-label levodopa could be added at any time during the study. Sixty-six percent of patients in the ropinirole group and 36% in the levodopa group received open-label levodopa supplementation. After 5 years of treatment, patients in the ropinirole group were receiving a mean daily dose of 16.5 mg of ropinirole plus 427 mg of open-label levodopa, and those in the levodopa group were receiving 753 mg of levodopa. Patients randomized to the ropinirole group had a significantly reduced risk for development of dyskinesia, regardless of whether or not they received open-label levodopa supplementation ($p<0.0001$; figure 10A).[153,188] Dyskinesias developed in 40/88 (45%) patients in the levodopa group compared to only 36/177 (20%) ropinirole-treated patients (odds ratio 3.9:1). When the analysis was restricted to patients who were able to remain on monotherapy and did not require open-label levodopa supplementation, only 5% of ropinirole-treated patients developed dyskinesia compared to 36% of those receiving levodopa monotherapy (odds ratio 15:1; $p<0.001$). The risk for development of disabling dyskinesias or motor fluctuations in the two groups yielded similar results in favor of the ropinirole-treated patients. An extension study is under way attempting to further determine the long-term impact of initial treatment with ropinirole. Patients in both treatment groups experienced benefits on the motor and ADL subscales of the UPDRS, although there were minor differences favoring levodopa (figure 11A).[153] It is difficult to explain these findings because patients in both groups could have received supplemental open-label levodopa at any point during the study if either the physician or the patient felt that additional treatment was necessary. Furthermore, early withdrawals were not different in the two groups (27% of ropinirole patients and 33% of levodopa patients). It is possible that the UPDRS does not completely capture all features related to parkinsonian disability. In this regard, it is noteworthy that dopamine agonists have antidepressant effects.[226]

Another study (the CALM-PD study) compared initial treatment of early PD patients with the dopa-



*$p < 0.001$

Figure 8. Percentage of parkinsonian patients demonstrating greater than 30% reduction in UPDRS score with ropinirole or levodopa at 6 months by Hoehn and Yahr stage. Ropinirole provides comparable benefits to levodopa in patients with Hoehn and Yahr stages I and II. Data from Rascol et al.[224] (Reproduced with permission from Olanow and Koller.[2])

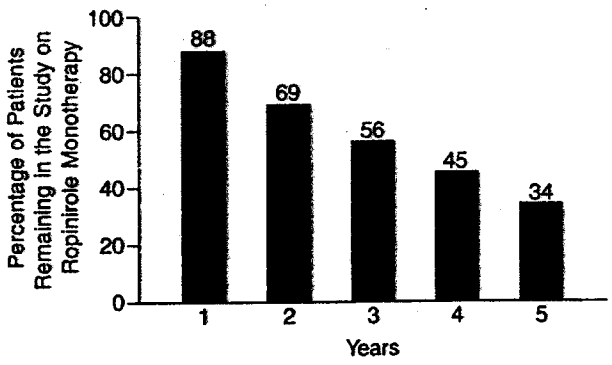


Figure 9. Percentage of patients remaining on ropinirole monotherapy by year during a 5-year double-blind comparison of levodopa and ropinirole in early PD. Approximately 50% of patients could be maintained on ropinirole monotherapy for 3 years and more than 30% for 5 years. Data from Rascol et al.[153]

mine agonist pramipexole versus levodopa in a double-blind study that was designed to evaluate the risk for development of motor complications.[154] A total of 301 untreated PD patients who needed dopaminergic therapy were randomized to receive either pramipexole or levodopa and were followed for a mean of 24 months. Provisions were made for blinded adjustments of experimental therapy and supplementation with open-label levodopa if deemed necessary, as in the ropinirole study. Forty-eight percent of patients in the pramipexole group required supplementation with open-label levodopa versus 36% in the levodopa group. After approximately 2 years of treatment, patients in the pramipexole group were receiving a mean daily dose of 2.78 mg of pramipexole and 264 mg of supplemental levodopa. Patients randomized to initiate therapy with levodopa received a mean total of 509 mg of levodopa per day. The primary end point was the time to the first occurrence of any of three motor complications: dyskinesia, wearing off, or "on–off" effects. In this study, the risk for development of a motor complication was greater in patients assigned to levodopa than for those randomized to pramipexole ($p<0.001$; see figure 10B).[154] Fifty-one percent of subjects assigned to initial treatment with levodopa reached the primary end point compared with only 28% of subjects randomized to initial treatment with pramipexole (hazard ratio 0.44; $p<0.001$). In comparison to patients assigned to levodopa, pramipexole-treated patients had reduced dyskinesia (10% versus 31%; $p<0.001$), reduced wearing-off effects (24% versus 38%; $p=0.009$), and reduced "on–off" effects (1% versus 5%; nonsignificant). As in the ropinirole study, the mean improvement in UPDRS motor scores was greater in the levodopa group than in the pramipexole group (see figure 11B).[154] Here, too, additional open-label levodopa could have been added if either the physician or the patient felt that it was necessary. This also raises a question as to whether dopamine agonists provide quality-of-life (QOL) benefits that are not captured by the UPDRS. Indeed, a double-blind controlled trial demonstrated that pramipexole provided antidepressant effects equal to those of fluoxetine (Prozac) in non-PD patients.[226] An extended, controlled study of this cohort is under way to determine the longer-term impact of initial pramipexole therapy compared to initial levodopa therapy.

Partial results are available from the cabergoline study.[225] As in the other dopamine agonist studies, the frequency of motor complications was reduced in patients randomized to receive the agonist versus levodopa. A total of 34% of patients randomized to receive levodopa developed motor complications over 3 to 5 years of follow-up compared to 22% of those who received cabergoline ($p<0.02$). The risk for development of a motor complication during treatment with cabergoline was more than 50% lower than with levodopa. Both treatment groups demonstrated improved motor and ADL scores, but again, benefits were slightly superior in the levodopa group.

Each of these studies has demonstrated that initiation of PD treatment with a dopamine agonist is associated with a reduced risk for development of motor complications in comparison with levodopa, and that this risk is further reduced if levodopa supplementation can be avoided entirely. Motor benefits on the UPDRS scale are slightly greater in levodopa-treated patients, but the clinical significance of this finding is not known because patients could have received additional levodopa therapy had they or their physician felt it was necessary. Importantly, some patients received short-term treatment with levodopa before entry into these studies. It will be interesting to determine if the small group of patients on ropinirole or pramipexole monotherapy who did experience motor complications had previously

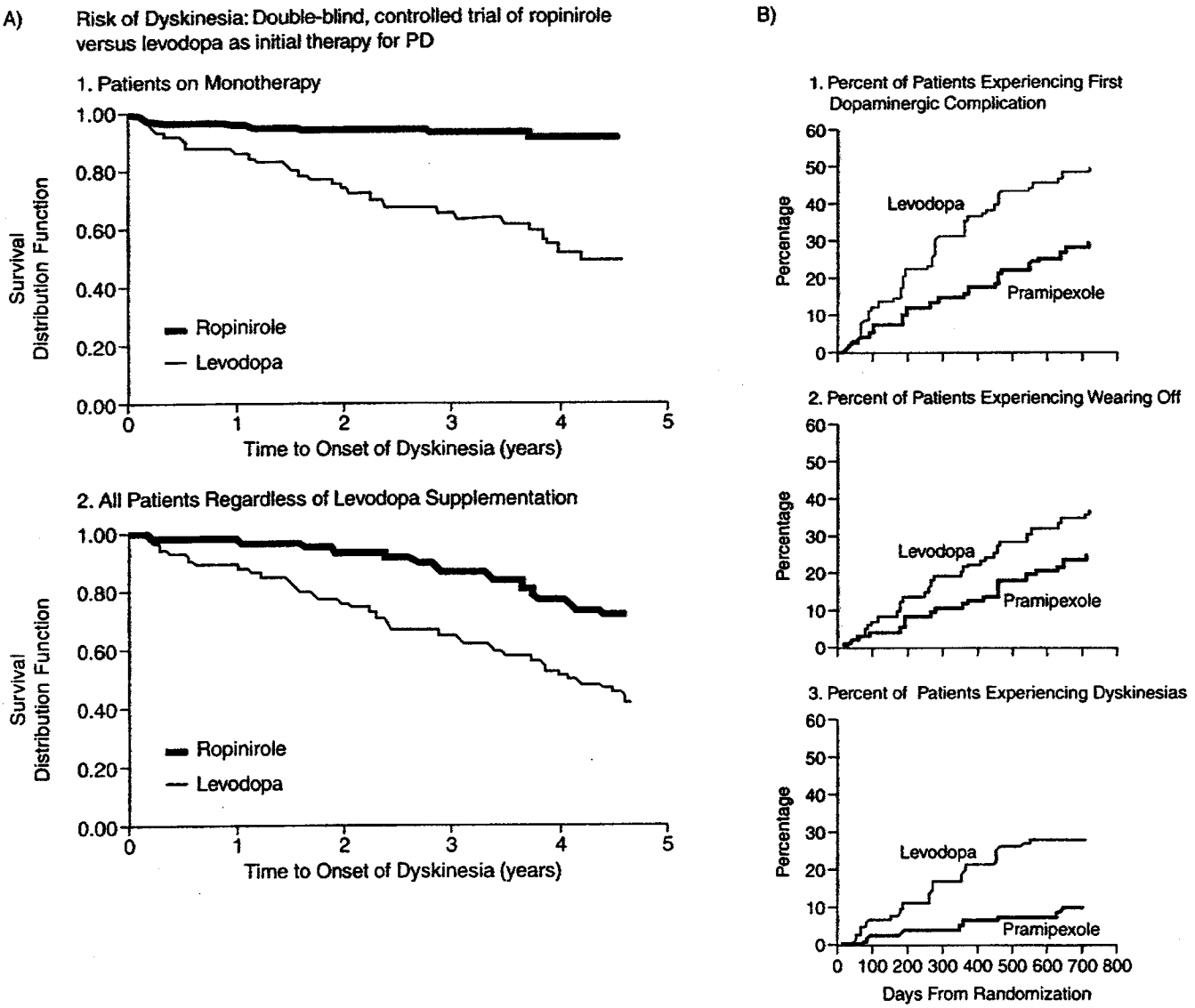


Figure 10. (A) Proportion of PD patients who remained dyskinesia-free after initiating therapy with levodopa vs ropinirole. (1) Patients remaining on ropinirole or levodopa monotherapy throughout study. There was a reduced risk for development of dyskinesias in ropinirole-treated patients; $p < 0.0001$. *(2) All patients (with or without levodopa supplementation). The introduction of levodopa is associated with an increased risk for development of dyskinesia even in patients receiving initial therapy with ropinirole. Data from Rascol et al.[153] (Reproduced with permission from Olanow.[188]) (B) Proportion of patients experiencing specific dopaminergic side effects with levodopa or pramipexole in a double-blind comparative trial. The onset of first dopaminergic complication (i.e., the first occurrence of "wearing off," dyskinesias, or "on-off" fluctuations) (top) was lower in the pramipexole-treated group than in those treated with levodopa. Compared with the levodopa-treated group, the pramipexole-treated group experienced less "wearing off" (middle) and dyskinesias (bottom). (Reproduced with permission from the Parkinson Study Group.[154])*

been exposed to levodopa and were therefore primed for these events to occur.

There is also a growing body of information suggesting that dopamine agonists may have neuroprotective effects in PD.[90] Dopamine agonists can protect cultured dopaminergic neurons from the toxic effects of levodopa[227,228] and dopaminergic nigral neurons from the adverse effects of aging[229] and 6-OHDA toxicity.[91] Moreover, ropinirole has been shown to protect nigral neurons and to improve survival of transgenic SOD mutant mice.[230] The mechanism by which dopamine agonists provide a neuroprotective effect in PD is unknown. It may relate to their capacity to (a) reduce the need for levodopa and thereby minimize the formation of levodopa-mediated oxidative metabolites, (b) stimulate D_2 autoreceptors so as to decrease dopamine synthesis and metabolism,[231,232] (c) exhibit antioxidant effects and scavenge free radicals,[91,228,233] (d) provide receptor-mediated anti-apoptotic effects,[228] and (e) restore striatal dopaminergic tone and thereby suppress glutamate overactivity in STN neurons and the risk for STN-mediated excitotoxicity.[93] Double-blind clinical trials using clinical and neuro-

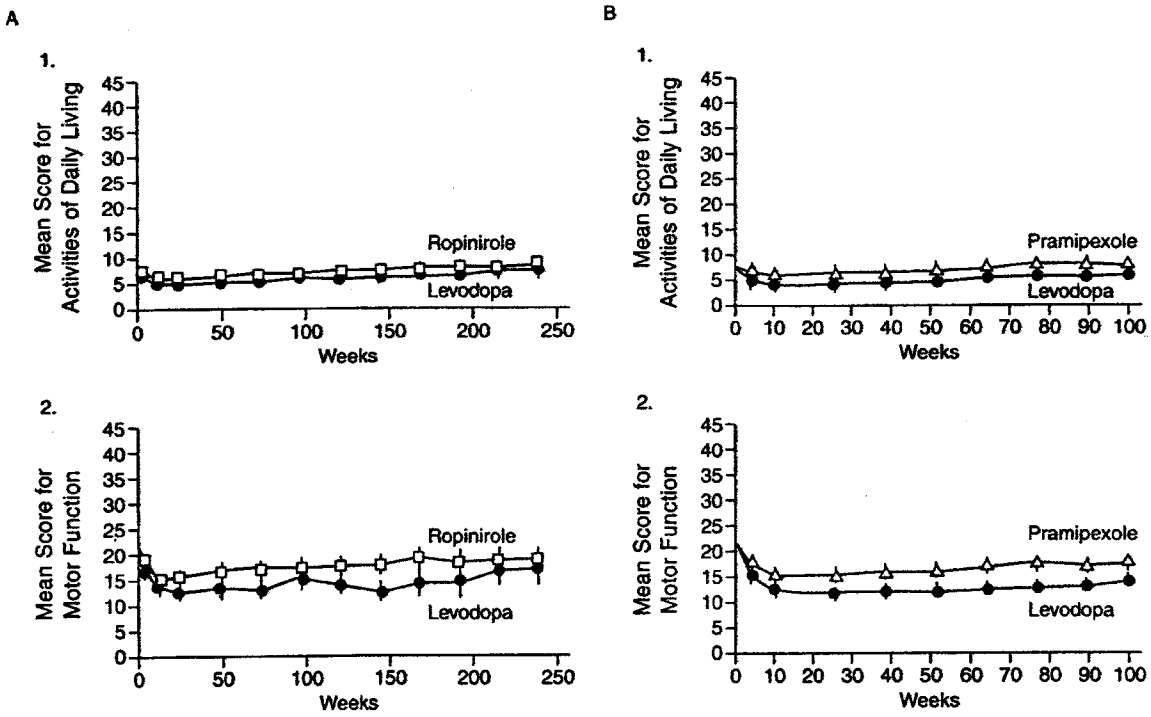


Figure 11. Mean UPDRS scores for activities of daily living (top) and motor function (bottom) in patients randomized to receive initial therapy with either ropinirole (A) or pramipexole (B) vs levodopa in randomized, double-blind comparative studies. Patients in either group could have received supplemental, open-label levodopa. UPDRS scores improved slightly more in patients randomized to initial therapy with levodopa vs either of the dopamine agonists. These results are difficult to interpret because patients in all groups could receive as much open-label levodopa as deemed necessary and drop-out rates were similar in all groups. (A adapted from data published in Rascol et al.[153]; B adapted with permission from the Parkinson Study Group.[154])

imaging end points are under way that are designed to compare ropinirole, pramipexole, and pergolide to levodopa as putative neuroprotective agents. It is hoped that these trials will provide information on the capacity of dopamine agonists to alter the rate of disease progression in comparison to levodopa.

The acute side effects of dopamine agonists are similar to those observed with levodopa. They include nausea, vomiting, postural hypotension, and psychiatric symptoms. They tend to occur with the initiation of treatment and to abate as tolerance develops over several days to weeks. Most movement disorder experts initiate dopamine agonists at a low dose and titrate gradually to the desired clinical response (see table 4 for therapeutic dose ranges). The use of domperidone, where available, minimizes these side effects and enables more rapid titration. Neuropsychiatric problems, specifically hallucinations and psychosis, are more common with agonists than with levodopa in most studies and are particularly prone to occur in elderly or cognitively impaired patients (see section on Neuropsychiatric Problems). Erythromelalgia, pulmonary or retroperitoneal fibrosis, and Raynaud's-like phenomena have been described in association with the ergot-derived dopamine agonists,[234] but these are relatively uncommon and may occur less frequently with the new non-ergot agonists.

Episodes of suddenly falling asleep while at the wheel of a motor vehicle have been described in a case report of eight PD patients who received the dopamine agonists pramipexole and ropinirole.[235] The authors termed these episodes "sleep attacks" because they were reported to have occurred without warning. It is now evident that such events are more common than was previously appreciated and that they can be associated with any dopaminergic drug, including levodopa.[236,237] The notion that these episodes are sleep attacks has been questioned,[238] because sleep episodes without antecedent sedation are not known to occur under physiologic or pathologic conditions, and indeed the term has been abandoned in narcolepsy.[239] It has been proposed that these episodes represent an extreme form of somnolence related to the sleep disturbances that are so common in PD, coupled with the propensity of dopaminergic drugs to induce dose-related sedation.[238] Approximately 80–90% of PD patients suffer sleep disturbances. These can be related to aging, insomnia, fragmented sleep, PD motor disturbances, medication effects, and a variety of sleep disorders.[240] In addition, dopaminergic medications are known to have dose-related sedative side effects.[153,154,199,220] Sleepiness in patients reported to have fallen asleep at the wheel may have gone unnoticed because subjective estimates of sleepiness are often unreliable

***Therapeutic Breakout 3** Dopamine agonists*

Advantages
Antiparkinsonian effects when used as monotherapy or as an adjunct to levodopa
Reduced risk for developing levodopa-related motor complications
Do not generate oxidative metabolites
Levodopa-sparing effect
Potential neuroprotective benefits
Disadvantages
Neuropsychiatric side effects (especially hallucinations and psychosis)
Agonist-specific side effects (erythromelalgia, ankle edema)
Sedative side effects
Do not completely prevent development of levodopa-related motor complications
Do not treat all features of PD, such as freezing, postural instability, autonomic dysfunction, dementia
Do not stop disease progression

and patients may have been amnestic for the drowsiness that antedated sleep.

To detect sleepiness, it is preferable to utilize scales such as the Epworth sleepiness scale,[241] which assesses the propensity to experience unintended sleep episodes and do not rely on subjective estimates of sleepiness. Studies to assess the frequency and causes of unintended sleep episodes in PD are under way. In the meantime, physicians should be aware of this potential problem in PD patients, and routine assessments of "sleepiness" should be performed on patients receiving dopaminergic medications. Management approaches include periodical evaluation of sleepiness, ruling out underlying sleep disorders, utilizing the lowest dose of a dopaminergic agent that provides satisfactory clinical control, and avoiding concomitant sedative medications.[242] Patients who have excessive daytime sleepiness should not drive until this problem has been resolved. See the section on Sleep Disorders for further discussion of this issue.

Few direct comparisons have been made among the different dopamine agonists. A double-blind crossover study demonstrated that pergolide and bromocriptine were of equal efficacy as adjuncts to levodopa in patients with advanced PD.[243] In a double-blind direct comparison between ropinirole and bromocriptine in untreated PD patients, ropinirole was shown to be superior (35% versus 28% improvement in UPDRS score; $p<0.05$).[244]

In summary, dopamine agonists are useful as adjuncts to levodopa in patients with advanced disease who already have motor complications. It has now been demonstrated that initiation of therapy with a dopamine agonist provides antiparkinsonian benefits and is associated with a reduced risk for development of motor complications compared to levodopa. However, dopamine agonists are less efficacious than levodopa, and levodopa supplementation is eventually required. A summary of the advantages and disadvantages of dopamine agonists is provided in therapeutic breakout 3.

COMT inhibitors. Levodopa is peripherally metabolized by aromatic amino acid decarboxylase (AADD) and COMT (figure 12). For the past 25 years, levodopa has been routinely administered in combination with a decarboxylase inhibitor to prevent its peripheral metabolism to dopamine. However, even when levodopa is administered with a decarboxylase inhibitor, the drug is converted by peripheral COMT to the inert metabolite 3-*O*-methyldopa (3-OMD), so that only 10% of a given dose reaches the brain intact.[245] Two drugs that inhibit COMT, tolcapone (Tasmar) and entacapone (Comtan), have been introduced to the market as adjunctive therapy to levodopa for treatment of PD. Both COMT inhibitors exert their therapeutic effect by inhibiting the peripheral metabolism of levodopa and thereby increasing its availability to the brain. They also reduce the formation of 3-OMD, which potentially can compete with levodopa for transport into the brain through the large neutral amino acid (LNAA) pathway. Tolcapone inhibits both peripheral and, to a lesser extent, central COMT, whereas entacapone acts only in the periphery.

Tolcapone and entacapone in clinically relevant doses inhibit erythrocyte COMT activity by 80–90% and 50–75%, respectively.[246,247] Pharmacokinetic studies demonstrate that both agents increase the plasma levodopa elimination half-life by approxi-

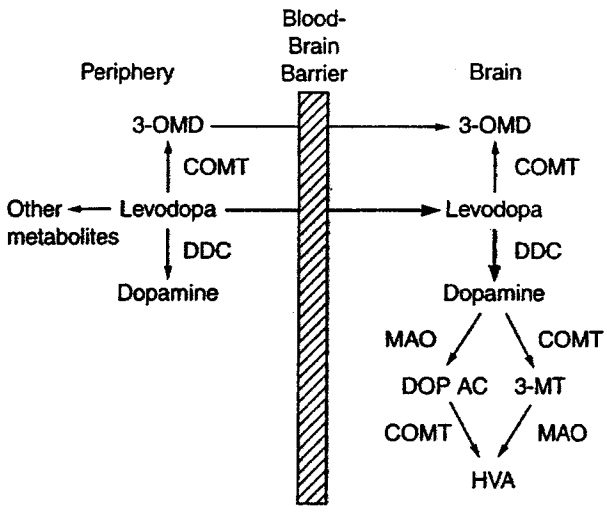


Figure 12. Schematic of levodopa metabolism. 3-MT = 3-methoxytyramine; 3-OMD = 3-O-methyldopa; COMT = catechol-O-methyltransferase; DDC = dopa decarboxylase; DOPAC = 3,4,-dihydroxyphenylacetic acid; HVA = 3-methoxy-4-hydroxyphenylacetic acid or homovanillic acid; MAO = monoamine oxidase. Peripherally administered levodopa is metabolized by both DDC and COMT. DDC and COMT inhibition can be used in conjunction with levodopa to reduce peripheral metabolism and increase brain availability.

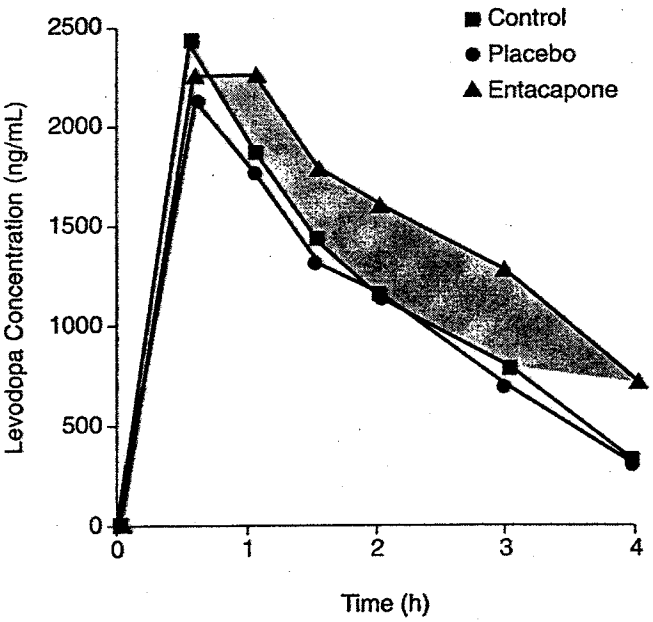


Figure 13. Mean plasma concentration of levodopa after an individual oral dose of levodopa/decarboxylase inhibitor (benserazide or carbidopa) alone (control) and after 4 weeks of concomitant placebo or entacapone in 23 PD patients. Area under the curve (AUC) is increased with the addition of a COMT inhibitor. COMT inhibition is associated with prolongation of levodopa elimination half-life and increased AUC without change in C_{max} and T_{max}. (Reproduced with permission from Ruottinen and Rinne.[250])

mately 50% and the area under the curve (AUC) by 75% without causing a corresponding rise in either the maximal plasma concentration (C_{max}) or the time to reach maximal plasma concentration (T_{max})[248,249] (figure 13).[250] These effects can be seen when the COMT inhibitor is administered in conjunction with either regular or controlled-release Sinemet. Chronic administration of levodopa with the COMT inhibitor entacapone provides increased interdose, trough, and mean levodopa concentrations but reduced peak levels.[251] Therefore, giving levodopa in combination with a COMT inhibitor results in smoother plasma levodopa levels and enhanced and more continuous brain availability compared to levodopa administered alone. This results in enhanced and more continuous brain availability of levodopa. This can be illustrated with FD PET studies that demonstrate increased striatal uptake when levodopa/carbidopa is administered with a COMT inhibitor (figure 14).[252] Therefore, administration of levodopa with a COMT inhibitor has the potential to deliver levodopa to the brain in a predictable and stable fashion, thereby decreasing the fluctuations in levodopa concentrations that are seen when levodopa is administered alone and which are believed to be associated with the development of motor complications.

These pharmacokinetic effects translate into clinical benefits for PD patients. Double-blind, placebo-controlled trials demonstrate that both tolcapone and entacapone provide increased "on" time, decreased "off" time, and improved motor scores in PD patients who suffer motor fluctuations (figure 15).[253-257] Periods in which patients experience poor motor function ("off" time) are reduced by 26 to 40%, and periods in which patients have good motor function ("on" time) are increased by 15–25%. In one placebo-controlled study comparing entacapone to placebo as an adjunct to levodopa/carbidopa in PD patients with motor fluctuations, mean daily "on" time was increased by 1.5 hours and the mean duration of the "on" response after each dose of levodopa was increased by 34 minutes in entacapone-treated patients[250,254] (see figure 15). This benefit was associated with a 16% reduction in the mean daily dose of levodopa. Similar results have been observed with tolcapone, for which double-blind, placebo-controlled studies show that tolcapone treatment decreased the duration of "off" time by 26 to 50% and the daily dose of levodopa by 29 to 40%.[256,258] Benefits with COMT inhibitors have also been observed in stable PD patients who have not yet begun to experience motor fluctuations. Two double-blind, placebo-controlled studies in PD patients with stable responses to levodopa demon-

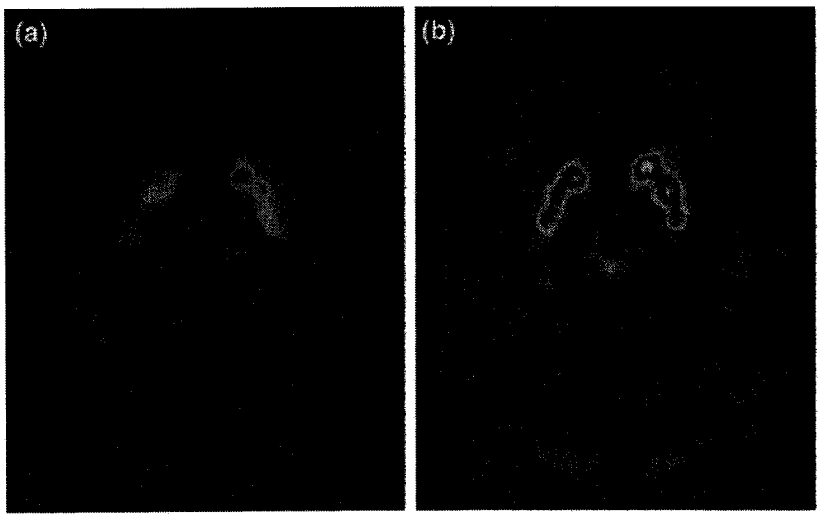


Figure 14. PET scan in which levodopa/carbidopa is administered without (a) and with (b) the COMT inhibitor entacapone. COMT inhibition is associated with increased FD uptake, reflecting increased brain availability of a given dose of levodopa. Data from Sawle et al.[252] (Reproduced with permission from Olanow et al.[188])

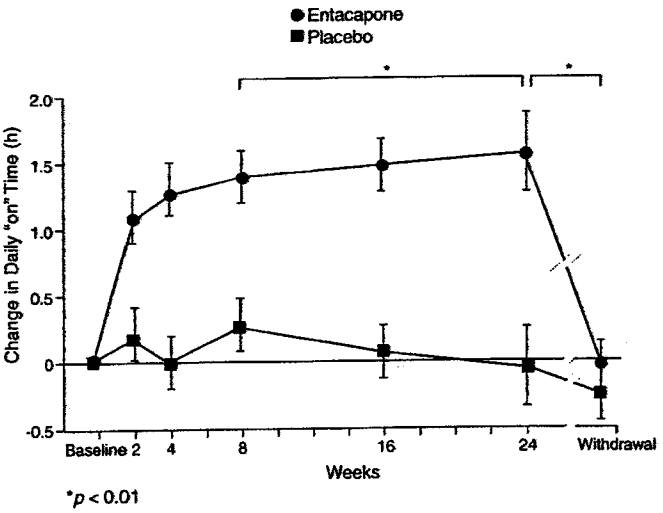


Figure 15. Double-blind controlled trial showing improvement in "on" time in patients randomized to treatment with levodopa vs levodopa plus entacapone. Entacapone treatment is associated with increased "on" time compared with placebo and benefits disappear rapidly after withdrawal. (Adapted with permission from Rinne et al.[254])

strated that those randomized to receive tolcapone therapy had improved ADL and motor scores and required lower levodopa doses in comparison to placebo-treated patients.[259,260]

In addition to the benefits that have been demonstrated in fluctuating and stable PD patients, there is increasing interest in the notion that the administration of levodopa with a COMT inhibitor from the time it is first introduced might reduce the risk that levodopa will induce pulsatile stimulation of striatal dopamine receptors and consequent motor complications.[258] This concept is based on the increasing body of information suggesting that the short half-life of levodopa is associated with the development of motor complications and that, by extending the half-life of levodopa with a COMT inhibitor, the risk for motor complications might be reduced (see sections on Motor Complications of Levodopa and Dopamine Agonists). As discussed above, studies in parkinsonian monkeys and in PD patients have noted that relatively long-acting dopamine agonists are less prone to induce motor complications than short-acting formulations of levodopa.[17] However, almost all PD patients treated with dopamine agonist monotherapy eventually require levodopa supplementation.[153,154] The introduction of levodopa in agonist-treated, MPTP-treated monkeys and PD patients is associated with an increase in the frequency of dyskinesia,[153,188] even though it remains less than in animals or patients treated with levodopa alone (see figures 6 and 10). This raises the possibility that introduction of levodopa with a COMT inhibitor to provide more stable levels of plasma levodopa might diminish the likelihood that levodopa will induce pulsatile stimulation of dopamine receptors and thereby reduce the risk for motor complications (figure 16).[188] Clinical trials to test this hypothesis are in the planning stage.

Side effects associated with the use of COMT inhibitors are primarily dopaminergic (dyskinesia and, less often, nausea, vomiting, hypotension, and neuropsychiatric problems) and reflect increased levodopa availability to the brain. These adverse reactions, especially dyskinesias, tend to occur within the first day or two of starting the COMT inhibitor and can usually be controlled by reducing the dose of levodopa by approximately 15 to 30%. Patients should be advised to notify their physician if there is an increase in dyskinesia or other dopaminergic side effects, particularly if they already have dyskinesia when the COMT inhibitor is introduced. In these circumstances, it is important to appreciate that the dopaminergic side effects should be treated by downtitrating the dose of levodopa, not the dose of the COMT inhibitor. Severe and explosive diarrhea may occur in 5 to 10% of tolcapone-treated patients after a latency of several weeks or months and usually necessitates discontinuing therapy. Both diarrhea and constipation have been described with entacapone, but these are much milder and do not usually require discontinuation of therapy. Discoloration of urine resulting from the accumulation of a drug metabolite may occur with either of the COMT inhibitors. This is harmless but may be a source of concern to the patient and caregiver if they are not so informed.

A more important problem is the potential of tolcapone to induce hepatic toxicity. Although liver toxicity was not detected in preclinical toxicology studies, liver enzyme elevations were observed in 1–3% of tolcapone-treated patients in clinical trials. However, none experienced clinical evidence of liver dysfunction. As a result of these findings, periodic monitoring of liver function was required at the time of drug approval. Four cases of liver dysfunction leading to death in three individuals have subse-

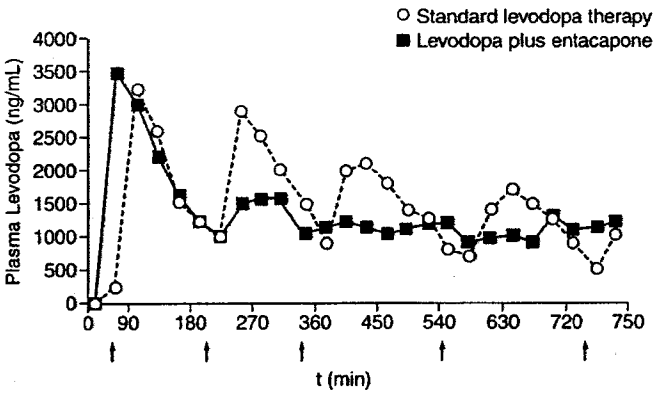


Figure 16. Plasma levodopa levels in a patient with fluctuating PD during standard levodopa monotherapy or combination therapy with levodopa plus entacapone. Fluctuations in plasma levels were minimized with combination therapy. Arrows indicate doses of levodopa. (Courtesy of F. Stocchi. Reproduced with permission from Olanow.[188])

quently been attributed to tolcapone therapy.[261,262] These observations have caused withdrawal of the drug from the market in Europe and Canada, as well as the issuance of a black box warning in the United States.[263,264] Although the drug still can be employed in the United States, liver function must be monitored every 2 weeks during the first year of use and periodically thereafter. Furthermore, the drug must be discontinued if liver enzyme levels are elevated above normal limits on even a single occasion. Although some consider the reaction of federal agencies to be excessive, for all practical purposes the drug is no longer employed. Fortunately, there is no evidence of liver dysfunction in patients treated with entacapone.[265] Preclinical toxicology studies showed no evidence of liver damage, liver enzymes were not elevated in comparison to placebo in clinical trials, and no cases of liver dysfunction attributed to entacapone have been reported during postmarketing surveillance of more than 100,000 patients. For these reasons, liver monitoring is not required with entacapone in any of the countries in which it is approved.

Tolcapone is administered in doses of 100 or 200 mg tid. The 200-mg dose provides greater efficacy. Entacapone is administered in doses of 200 mg with each dose of levodopa. Either agent can be initiated without titration and side effects can be addressed if and when they occur. Both tolcapone and entacapone have no antiparkinsonian effect when administered in the absence of levodopa.

In summary, double-blind controlled studies with COMT inhibitors demonstrate clinical benefits in PD patients with motor fluctuations and those with stable responses to levodopa. Combining levodopa with a COMT inhibitor from the time it is first introduced may reduce the risk for development of motor complications, and this concept is now being explored. If this proves to be the case, it would imply that levodopa should always be administered with a COMT inhibitor in much the same way as a decarboxylase inhibitor.[266] A single tablet containing levodopa, a dopa decarboxylase inhibitor, and a COMT inhibitor might be the best and most practical way to administer levodopa. COMT inhibitors are easy to administer and are usually well tolerated. The most common side effect is dyskinesia, reflecting the increase in central dopaminergic activity. Usually it is only a problem in patients who already have dyskinesia and generally can be readily controlled by a 15 to 30% reduction in the levodopa dose. Physicians should be aware of this side effect because it tends to occur within 1 to 2 days of initiating a COMT inhibitor and may require an immediate dose adjustment. Because of the risk for liver toxicity, the use of tolcapone has been severely restricted, and entacapone has emerged as the COMT inhibitor of choice. The advantages and disadvantages of the COMT inhibitors are summarized in therapeutic breakout 4.

Therapeutic Breakout 4 *COMT inhibitors*

Advantages
No titration; easy to administer
Decreased "off" time, increased "on" time, and enhanced motor responses in patients with levodopa motor fluctuations
Improved motor and ADL scores in stable levodopa responders
May reduce risk for motor complications if used from onset of levodopa therapy
Disadvantages
Dopaminergic side effects, especially dyskinesia
Discoloration of urine
Tolcapone associated with explosive diarrhea in 5–10% of cases
Tolcapone associated with liver toxicity

Other antiparkinsonian drugs

Anticholinergics. Anticholinergic agents have been used in the treatment of PD since the middle of the 19th century,[267] and anticholinergic agents such as trihexyphenidyl (Artane), benztropine (Cogentin), biperiden (Akineton), orphenadrine (Disipal), and procyclidine (Kemadrin) are still employed even in the era of levodopa and dopamine agonists.[268] It long has been believed that there is a balance between dopamine and acetylcholine neurotransmission in the basal ganglia, and cholinergic drugs have been shown to exacerbate and anticholinergic drugs to improve parkinsonian symptoms.[269] The precise mechanism of action of anticholinergic drugs in PD is not known, although cholinergic interneurons in the striatum are known to bear D_1 and D_5 dopamine receptors,[270] and although they are relatively small in number they have many synaptic connections and therefore have the potential to exert powerful effects on medium spiny strial neurons.[271]

Anticholinergic drugs are typically used in younger PD patients (i.e., ≤60 years of age) in whom resting tremor is the dominant clinical feature and cognitive function is preserved. Anticholinergic drugs are of little value in the treatment of other parkinsonian features, such as rigidity, akinesia gait dysfunction, or impaired postural reflexes.[272] In some patients, tremor may respond particularly well to anticholinergic agents, but levodopa is probably more effective for the control of tremor.[273] Trihexyphenidyl is the most widely used of the anticholinergic drugs, but there is no evidence to suggest that any single drug in this class is superior to another in terms of therapeutic efficacy or side effects. Trihexyphenidyl typically is initiated at a dose of 0.5 to 1 mg twice a day (bid) and is increased gradually to a dosage of approximately 2 mg tid, as tolerated. Benztropine is the second most commonly used anticholinergic drug and is typically prescribed in doses of 0.5 to 2 mg bid. Peripherally acting anticholinergic agents such as propantheline (Pro-Banthine) or glycopyrrolate (Robinul) may be useful in treating sialorrhea.

Adverse effects of central-acting anticholinergic drugs are common and often limit their use. The

most important of these are memory impairment, confusion, and hallucinations. These are most likely to occur in older individuals, but even younger parkinsonian patients without evident cognitive impairment can experience neuropsychiatric dysfunction during anticholinergic treatment. Even in patients who appear to be tolerating the drugs well, improvement in short- and long-term memory has been demonstrated after their withdrawal.[268] Other CNS side effects include sedation and dysphoria. Dyskinesias have been reported with anticholinergic therapy.[140] Interestingly, these tend to be oro–buccal in distribution and resemble those seen in tardive dyskinesia. It has also been suggested that the long-term use of anticholinergic agents may promote the development of levodopa-induced dyskinesias.[274]

Peripheral side effects include dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia. Particular caution should be exercised in the use of anticholinergic medications in the presence of prostatic hypertrophy or closed-angle glaucoma because these conditions may be exacerbated. Milder side effects, such as dry mouth and blurred vision, may subside with continued treatment and, although a nuisance for patients, do not usually limit therapy. Baseline cognitive evaluations, psychiatric history, and supine and standing blood pressure should be obtained in older patients before initiation of anticholinergic therapy.

Because of the many side effects associated with the use of anticholinergic medications, many physicians prefer not to use these drugs, particularly in the elderly. Anticholinergic drugs should be discontinued gradually to avoid withdrawal effects and acute exacerbation of parkinsonism, even in patients in whom there appears to have been no clinical response.[275]

In summary, anticholinergic agents are sometimes used in the treatment of younger PD patients in whom resting tremor is the predominant feature. Anticholinergic therapy in older patients, in patients without tremor, and in demented patients is not indicated. Because of the side-effect profile and the limited efficacy associated with these drugs, many physicians are reluctant to employ them. If they are used and it is decided to stop them, they must be withdrawn gradually. A summary of the advantages and disadvantages of anticholinergic drugs is provided in therapeutic breakout 5.

***Therapeutic Breakout 5** Anticholinergics*

Advantages
Some antiparkinsonian efficacy (particularly with respect to tremor)
Peripherally acting agents may be useful in treating sialorrhea
Disadvantages
Relatively ineffective for the more disabling features of PD
Cognitive side effects
May be associated with withdrawal effects
Troublesome muscarinic side effects

Amantadine. Amantadine (Symmetrel) is an antiviral agent that was discovered by chance to have antiparkinsonian activity.[276] Its mechanism of action in PD has not been established, but it was originally believed to work by increasing dopamine release, by blocking dopamine reuptake, by stimulating dopamine receptors and, possibly, by anticholinergic effects.[277,278] In uncontrolled studies, approximately two-thirds of patients who received amantadine show improvement in akinesia, rigidity, and tremor.[276,279] These benefits have been confirmed in placebo-controlled trials[280,281] and have been reported when amantadine is used either as monotherapy or in combination with levodopa.[282] In one study, amantadine was found to be more effective than anticholinergic drugs with regard to akinesia and rigidity,[283] but it appears to be less effective with respect to tremor.[273] Early studies fostered the belief that benefit from amantadine was transient, with one-third of patients showing reduced benefit within 4–8 weeks of initiation of treatment. However, this view is not universally held, and many physicians believe that clinical benefits can be sustained.

Amantadine has a plasma half-life of about 10 to 28.5 hours and can be administered in dosages of 100 to 200 mg one to three times daily. Larger dosages appear to provide no additional benefit[284] and increase the likelihood of adverse effects. Amantadine is not metabolized and is excreted unchanged in the urine. Accordingly, patients with renal impairment should receive lower doses and should be monitored carefully for adverse effects. Amantadine is usually initiated at a dose of 100 mg daily for 1 week, followed by dosage increases as needed to 100 mg two or three times per day. Higher doses are not usually employed because of the risk for cognitive dysfunction (see below).

The most important side effects associated with amantadine are confusion, hallucinations, insomnia, and nightmares. These are more common in older patients but can occur in patients of any age. Peripheral side effects include livedo reticularis and ankle edema, although these are rarely severe enough to limit treatment. CNS toxicity is more likely to occur when amantadine is used in combination with other antiparkinsonian drugs. Dry mouth and blurred vision can occur and are presumed to be related to the peripheral anticholinergic effects of amantadine. Some patients experience a dramatic worsening of PD when amantadine is withdrawn. This may occur even when no evident clinical benefit has been detected, and may represent a withdrawal effect. For this reason, amantadine should be withdrawn gradually.

It has been proposed that amantadine, in addition to its other functions, acts as an *N*-methyl-D-aspartate (NMDA)-receptor antagonist.[285,286] Both in vitro and in vivo studies have demonstrated that NMDA receptor antagonists can protect dopaminergic neurons from excitotoxic damage,[75,287] suggesting that they might have neuroprotective effects in PD

***Therapeutic Breakout 6** Amantadine*

Advantages
Some antiparkinsonian efficacy
May have antidyskinetic effect in some patients
Possible neuroprotective effects
Disadvantages
Antiparkinsonian benefits are limited
Tolerance may develop
Cognitive side effects
Potential for withdrawal effects

where excitotoxicity has been implicated.[40,288,289] A retrospective clinical study has suggested that PD patients who have received long-term amantadine treatment have improved survival, implying that the drug might have altered the natural course of disease in these patients.[290] Chase and Oh[214] have also suggested that NMDA-receptor antagonists might have antidyskinetic effects. They proposed that levodopa-induced pulsatile stimulation of dopamine receptors on medium spiny striatal neurons induces abnormal phosphorylation of NMDA receptors, leading to glutamate-mediated plastic changes and the development of motor complications.[291] In support of this concept, they have shown that NMDA receptor antagonists, and specifically amantadine, can improve levodopa-induced dyskinesia in MPTP-treated monkeys[292,293] and PD patients.[294,295] However, the utilization of amantadine in these situations is limited by the propensity of the drug to cause cognitive impairment, especially in patients with advanced PD.

In summary, amantadine is used by some practitioners for treatment of early PD patients to delay the need for levodopa and possibly to provide some protective effects. It is less commonly employed in patients with advanced disease, although there is some evidence to suggest that it can provide antidyskinetic effects for some patients. Its use is limited by its potential for neuropsychiatric side effects. Further studies are necessary to better establish its role in the management of dyskinesia and any effect it might have on the natural history of PD. A summary of the advantages and disadvantages of amantadine is provided in therapeutic breakout 6.

Pharmacologic approach to patients with early PD

The issue of neuroprotection (algorithm 1). In approaching the patient with newly diagnosed PD, the first therapeutic issue that should be considered is neuroprotection. If an agent can be established to slow or halt PD progression, it should be introduced as soon as the diagnosis is made. Indeed, the development of a neuroprotective therapy for PD would spark an intensive search for disease markers that might permit preclinical diagnosis and the introduction of a disease-modifying therapy before the emergence of overt clinical signs and symptoms. At present, the best opportunity for detecting at-risk or preclinical PD patients is with gene screening or neuroimaging techniques that provide a surrogate marker of the number of nigral dopaminergic neurons or striatal terminals (see section on Diagnosis). At present, the drug that has been most widely studied as a putative neuroprotective agent in PD is selegiline. As described in the section on neuroprotection (see above), there is strong laboratory evidence to support the notion that selegiline (or its metabolite) can protect dopaminergic neurons in in vivo and in vitro models.[71] Clinical trials in PD patients demonstrate that selegiline delays the emergence of clinical dysfunction and the progression of parkinsonian signs and symptoms.[67,68] However, interpretation of these results is confounded by the symptomatic effect of the drug. It remains uncertain whether benefits obtained in clinical trials are due to selegiline protecting against the degeneration of nigral neurons or to the drug providing a symptomatic effect that masks the underlying degenerative process. Physicians are left with the choice of starting early PD patients on selegiline because of its potential to provide a disease-modifying effect or withholding it because it has not been established to provide protective effects in PD. Although there is some controversy about whether to use selegiline in the early stages of the disease, it is usually not employed in patients in more advanced stages in whom progression has already occurred and in whom the MAO-B inhibiting capacity of the drug can make dopaminergic side effects more difficult to control.

Vitamin E is probably harmless, but it did not provide any benefit to untreated PD patients in a dose of 2,000 IU per day in the DATATOP study.[67] There is a rationale for considering other putative neuroprotective agents, such as antioxidants, bioenergetics, antiglutamatergic, anti-inflammatory, and antiapoptotic agents, but none has been established to be effective in PD. Furthermore, agents such as vitamin C and β-carboline have antioxidant effects under some conditions but pro-oxidant effects under others. Therefore, they may adversely affect disease progression.[62] These agents therefore cannot be recommended until further trials have been performed and more data are available. Several drugs are now being tested for putative neuroprotective effects in prospective clinical trials. These include dopamine agonists (ropinirole, pergolide, pramipexole), riluzole, co-enzyme Q10, TCH-346, neuroimmunophillins, GDNF, and transplantation of dopaminergic cells. In addition, many of the other agents listed in table 1 are also being considered for clinical trial. It is likely that a greater number of possible neuroprotective agents would be tested if an outcome variable of disease progression could be defined that was acceptable to regulatory agencies. The determination that any intervention is neuroprotective and can slow the progression of the disease process would represent a major turning point in the management of this disorder and is eagerly awaited.

The issue of symptomatic therapy (algorithm 1). The next issue that must be addressed is that of symptomatic therapy. Most movement disorder specialists favor delaying the introduction of symptomatic therapy until the patient has begun to develop some degree of functional disability (see section on When To Initiate Symptomatic Therapy). This is an individual determination based on patient need and physician philosophy. For the past 30 years, levodopa has been the gold standard for the symptomatic treatment of PD because it is the most efficacious and enduring antiparkinsonian medication. Common practice was to initiate symptomatic therapy with levodopa combined with a decarboxylase inhibitor and then supplement with a dopamine agonist when the patient began to develop motor complications (dyskinesia and motor fluctuations). However, once motor complications have developed, they may be very difficult to control with medical therapies (see section on Management of Motor Complications) and frequently necessitate surgical interventions with their potential adverse effects (see section on Surgical Treatments).

In the past decade, a paradigm shift has begun to occur in favor of initiating symptomatic therapy with a dopamine agonist and adding levodopa as a supplement when dopamine agonist monotherapy can no longer provide satisfactory clinical control. This is based on the growing body of laboratory and clinical information suggesting that the origin of motor complications in PD is due to abnormal pulsatile stimulation of denervated dopamine receptors by short-acting dopaminergic agents such as levodopa.[158-160,170,296] This has led to the concept that initiation of treatment with more continuous dopaminergic stimulation might reduce the risk for motor complications associated with conventional levodopa treatment.[186-188] Studies in monkeys rendered parkinsonian with MPTP reveal that treatment with dopamine agonists provides motor benefits while avoiding the abnormal behavioral and molecular changes that are associated with levodopa therapy[17,178,179,296] (see figure 6). Moreover, in the MPTP-treated monkey model, early treatment with levodopa primes for the development of dyskinesia. A dopamine agonist that does not induce dyskinesia when administered to a drug-naive monkey can induce dyskinesia if the monkey has been exposed to even a single dose of levodopa.[17,216] Retrospective and/or open-label studies have long suggested that PD patients receiving dopamine agonists have fewer motor complications than patients receiving levodopa.[151,152,217,218,297]

A series of prospective, double-blind, controlled clinical trials have compared dopamine agonists to levodopa as initial symptomatic therapy for PD. These studies have demonstrated that patients randomized to initiation of therapy with a dopamine agonist (supplemented with levodopa if deemed necessary) have a reduced risk for development of motor complications compared to those randomized to receive levodopa alone[153,154,225] (see figure 10). Interestingly, improvement in UPDRS motor score was slightly greater in levodopa- than dopamine agonist-treated patients, but both treatment strategies provided comparable clinical benefits because patients in either group could have taken supplemental open-label levodopa if either the patient or physician felt it was necessary. This has raised the question of whether the UPDRS scale captures all aspects of functional disability in PD patients. Because reduced motor complications in comparison to levodopa have been observed with ropinirole, pramipexole, pergolide, and cabergoline, this probably reflects the relatively long plasma half-life of these dopamine agonists compared to levodopa. Studies to determine if dopamine agonists also can alter the natural rate of disease protection are ongoing.

On the basis of these data, it is clear that physicians now have a choice in deciding which dopaminergic medication to use when initiating symptomatic therapy for a PD patient. Levodopa has been traditionally used as the initial drug to treat PD and may provide enhanced motor benefits in comparison to dopamine agonists. However, there are now compelling reasons to consider initiating symptomatic therapy with a dopamine agonist (table 6), especially for young-onset patients who are at high risk for development of motor complications.[144-146] First, dopamine agonists are associated with a reduced risk for inducing motor complications in comparison to levodopa. Because motor complications represent a major source of disability to the majority of PD patients and frequently lead to consideration of surgical intervention, this is a major therapeutic advantage. Second, dopamine agonist monotherapy can provide antiparkinsonian effects that are comparable to those of levodopa in the early stages of PD[220-223] and these effects can be sustained for more than 3 years in the average patient.[224] Third, levodopa can be added to enhance clinical benefits when dopamine agonist monotherapy can no longer provide satisfactory control of parkinsonian features.[153,154] Fourth, dopamine agonists have putative neuroprotective effects. For these reasons, we believe that it is preferable to initiate symptomatic therapy with a dopamine agonist and supplement with levodopa when clinical features are no longer satisfactorily controlled, although this

Table 6 *Reasons to consider initiating therapy with a dopamine agonist*

Reduced motor complications compared with levodopa
Antiparkinsonian effect superior to placebo in early-stage PD
Antiparkinsonian effect comparable to levodopa in early-stage PD
Patients may be able to be maintained on dopamine agonist monotherapy for several years
Supplementation with levodopa provides clinical benefits comparable to levodopa alone but with reduced motor complications
Putative neuroprotective effects

approach is not recommended for all patients. Starting therapy with levodopa is still preferred in PD patients with cognitive impairment who may not tolerate dopamine agonists, in the elderly who have a reduced propensity to develop motor complications, and in those who are believed to suffer from atypical parkinsonism rather than PD.

Eventually, despite initial therapy with dopamine agonists, virtually all PD patients require levodopa to maintain satisfactory control of parkinsonian disability. Although levodopa plus a dopamine agonist is associated with reduced motor complications compared to levodopa alone, the addition of levodopa to an agonist increases the risk for motor complications compared to the dopamine agonist alone in both MPTP-treated monkeys and PD patients[153,154,179,188] (see figures 6 and 10). This has led to the idea that it may be preferable to use a COMT inhibitor with levodopa to increase its plasma half-life and reduce the risk that it will induce pulsatile stimulation of striatal dopamine receptors with consequent motor complications.[188,258] Laboratory and clinical studies to test this hypothesis are under way.

In considering treatment for patients with early PD, some other issues are as follows.

What is the role of anticholinergics and amantadine in early therapy? Most physicians use these drugs sparingly because of the risk for cognitive impairment, but they may have a role in young PD patients with minor parkinsonian features (especially tremor).

Are there differences between the different dopamine agonists? The few comparison studies that have been performed do not show clear-cut advantages between any of the currently employed dopamine agonists. In individual cases, one agonist may be preferable to another but, in general, it is probably best to utilize the agent with which the individual physician has the most experience. There are no data supporting the use of combined dopamine agonists as yet.

Is there any reason to push the dose of a dopamine agonist to higher levels than are currently recommended to maximally delay the introduction of levodopa? This issue has not been satisfactorily studied to provide an adequate answer to this question. On the other hand, if it can be established that exposure to even a small amount of regular levodopa primes for the development of motor complications, an argument could be made for trying to delay the introduction of levodopa for as long as possible. However, if COMT inhibitors reduce the risk for motor complications with levodopa use, then it will not be necessary to employ high doses of dopamine agonists, which can be associated with sedation and unintended sleep episodes[235] (see section on Sleep Disorders). At present, it is probably best to titrate the dopamine agonist to currently recommended doses and then supplement with levodopa rather than attempting to utilize doses higher than those currently recommended. As with all antiparkinsonian drugs, the lowest dose that provides a satisfactory response should be employed.

How do you manage patients who have already been started on levodopa therapy? There are as yet no data on the best way to manage this population of patients. Laboratory studies in MPTP-treated monkeys suggest that the risk for induction of motor complications by levodopa is reduced if it is combined with a dopamine agonist. Most experts today would supplement with a dopamine agonist rather than increase the levodopa dose in a patient already receiving levodopa. There is no information at this time to indicate whether having been on levodopa has primed for the induction of dyskinesia in PD, as occurs in monkeys, or to know if adding a dopamine agonist will diminish this risk. There is also no information on whether it is beneficial to replace levodopa with a dopamine agonist, and most movement disorder specialists would not do this at present.

Is initial therapy with levodopa coupled with a COMT inhibitor preferable to treatment with a dopamine agonist? This is an important question, but studies designed to address this issue have not yet been performed. The MPTP-treated monkey model has served us well in predicting clinical responses and could offer valuable insights into this question before human trials are initiated.

What is the role of Sinemet CR or Madopar HBS in the management of early PD? Two prospective, double-blind trials compared immediate- to controlled-release formulations of levodopa to determine if the longer half-life of the controlled-release formulation compared to regular levodopa might lead to reduced motor complications. No difference in prevalence or time to onset of motor complications was detected between the two treatment groups.[148-150] However, there are several factors that might explain why no benefit was observed with the long-acting preparation in these studies. First, controlled-release levodopa preparations have variable absorption and levels tend to accumulate over the course of the day. Therefore, they do not provide continuous plasma levodopa levels. Second, the administration of controlled-release formulations of levodopa in these studies may have been too infrequent (e.g., bid) to avoid fluctuations in plasma levels, and different results might have been obtained with more frequent dosing. For the present, there is no compelling reason to routinely employ controlled-release formulations of levodopa in early PD patients because the drug is more expensive than regular levodopa and there is no evidence that it provides additional benefit. However, it is possible that combining controlled-release formulations of levodopa with a COMT inhibitor may reduce the variability in its metabolism and provide a more constant, long-acting levodopa preparation than can be achieved with a COMT inhibitor and regular levodopa.

On the basis of existing basic science and clinical data, we have modified our previous algorithm for the treatment of early PD patients[2] to include the following elements:

- Ensure that the correct diagnosis has been made.
- Consider neuroprotective therapy as soon as the diagnosis is made.
- Initiate symptomatic therapy with a dopamine agonist in appropriate patients.
- Supplement with levodopa when dopamine agonist monotherapy can no longer provide satisfactory clinical control.
- Consider introducing supplemental levodopa therapy in combination with a COMT inhibitor to extend its elimination half-life and further reduce the risk of motor complications.

Factors that might influence the choice of initial therapy in PD include the following:

Age: Most neurologists favor introducing a dopamine agonist in younger patients (<70 years) but would start with levodopa plus a decarboxylase inhibitor in older patients because of concerns about cognitive dysfunction and because older patients are less likely to develop levodopa-related motor complications. Anticholinergic drugs and amantadine are specifically discouraged in older patients because of the risk of aggravating underlying mental function.

Cognitive impairment: Most neurologists would favor initiating treatment of PD symptoms with levodopa plus a decarboxylase inhibitor in patients with cognitive impairment, regardless of age. The immediate-release formulation of levodopa/carbidopa is simpler to initiate and to adjust in this population of patients, thereby avoiding some of the cumulative effects associated with controlled-release preparations and the psychiatric problems associated with dopamine agonists. In general, it is best to eliminate polypharmacy in cognitively impaired patients. Medications should be withdrawn or reduced in dose in a gradual and stepwise fashion based on their relative antiparkinsonian efficacy and their potential to aggravate mental function. In rank order, drugs should be discontinued as follows:

sedative medications;

anticholinergic medications and amantadine;

selegiline;

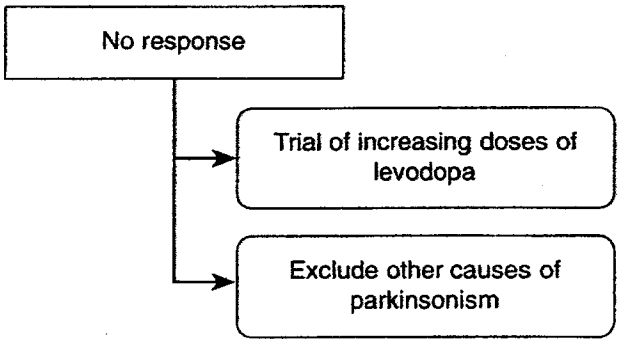
dopamine agonists; and

levodopa.

Disease severity: Many neurologists favor starting with levodopa plus a decarboxylase inhibitor in PD patients with severe disease. However, because disease severity is one of the factors that is believed to contribute to the development of motor complications,[170] this might be precisely the population of patients who would do best if started on a dopamine agonist.

Threatened loss of employment: Many neurologists would start with levodopa plus a decarboxylase inhibitor because they want a rapid response. However, a rapid response also can be obtained with a dopamine agonist, particularly if it can be co-administered with domperidone. Because patients who are still working are frequently younger individuals who are at greater risk for development of motor complications, it might be best to consider the long-term outcome before making a short-term therapeutic decision.

Cost: A major factor in selecting treatment for many patients is the cost of medication. Despite the potential for obtaining future benefits, current healthcare realities might dictate initiation of treatment with the least expensive antiparkinsonian medication. However, there are obvious financial and personal costs associated with the development of adverse events and the need for surgical interventions, and pharmacoeconomic studies specifically addressing these issues are warranted.

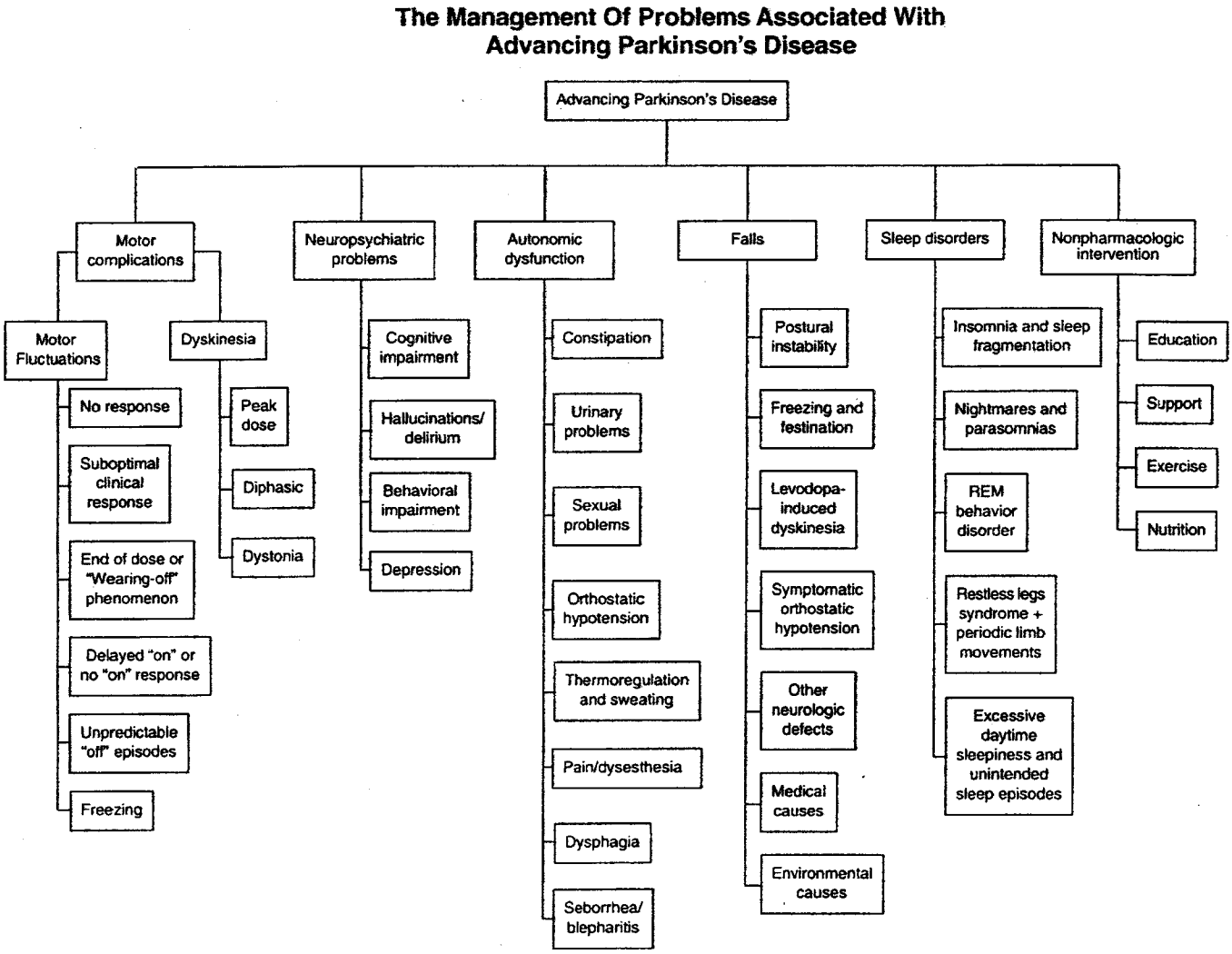


Breakout 1. Patients who fail to respond to levodopa may have an atypical parkinsonism. If this diagnosis is suspected, the dose of levodopa should be gradually increased until the patient responds to treatment or develops side effects. Many patients with atypical parkinsonism still show some benefit from small doses of levodopa. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

In summary, correct and early diagnosis and introduction of a neuroprotective agent are the first steps in managing early PD. When patients develop functional disability, increasing evidence argues in favor of initiating therapy with a dopamine agonist and supplementing with levodopa when agonist monotherapy can no longer provide satisfactory clinical control. In this way, PD patients can be provided with the desired clinical benefit and a reduced risk for development of motor complications. Combining levodopa with a COMT inhibitor from the time that levodopa is first introduced may further reduce the risk for motor complications.

Management of motor complications. This section provides strategies for the management of the motor complications associated with levodopa therapy.

Motor fluctuations No initial response. Some parkinsonian patients experience little or no benefi-

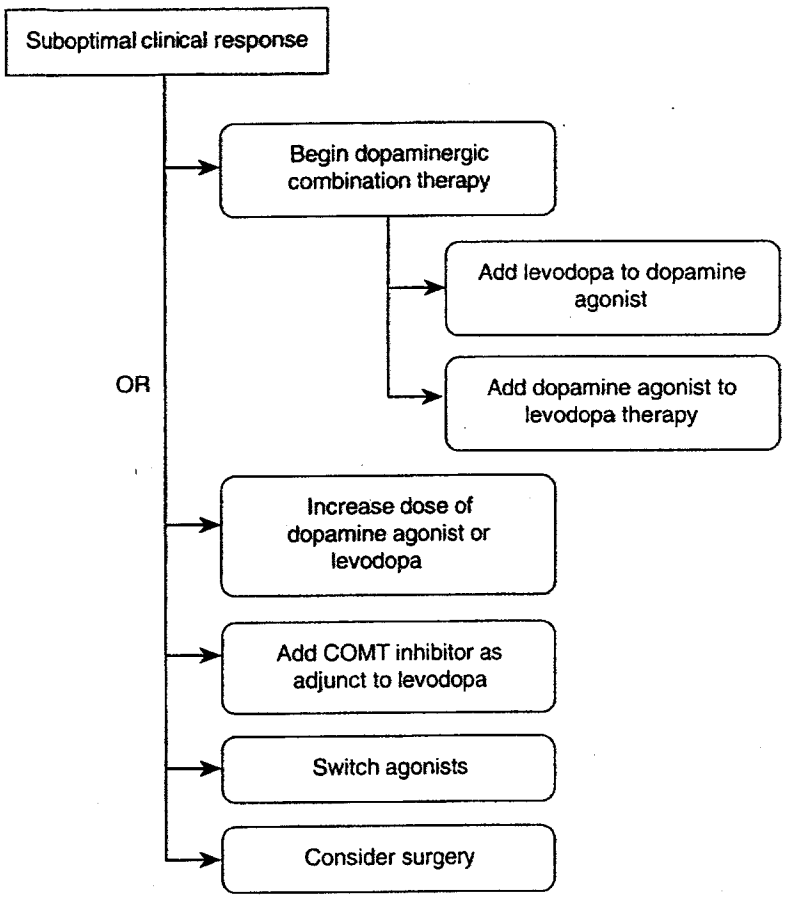


Algorithm 2. Management of problems associated with advancing Parkinson's disease.

cial response to levodopa or other dopaminergic therapy even when it is employed in high doses. Such patients probably do not have PD but rather an atypical parkinsonism, such as MSA or PSP, in which pathology is widespread, precluding the possibility of a response to a dopaminergic agent. An adequate trial of medication must be employed before concluding that the patient is a nonresponder (usually a dose of at least 1,000–1,500 mg of levodopa combined with a decarboxylase inhibitor; see breakout 1). Care must also be taken before concluding that a patient is a nonresponder in the early stages because it may be difficult to detect clinical improvement when features are mild, particularly if tremor is the primary feature. Neuroimaging, autonomic, ophthalmologic, and electromyographic studies may be helpful in trying to determine whether a patient has an atypical parkinsonism rather than PD. Patients who fail to respond to lower dosages of levodopa/carbidopa and who are suspected of having atypical parkinsonism should have the levodopa dosage gradually increased until they show a response or develop side effects.

Occasional PD patients require a daily levodopa dose of 1,000–1,500 mg before they show a response, and these patients should be given an opportunity to benefit from levodopa. Alternatively, patients with atypical parkinsonism may have some benefit from levodopa, particularly in the early stages of the disorder. Because the long-duration levodopa response takes several days to become fully manifest, patients should be maintained on the higher doses for approximately 1 week to enable the full effect to occur. Once it is determined that levodopa provides no meaningful benefit, the dose should be decreased to the lowest level that is useful to the patient. In these circumstances, it is preferable to employ the standard rather than the controlled-release formulation of levodopa.

Suboptimal clinical response. Patients who experience suboptimal motor control with dopamine agonist or levodopa monotherapy may be able to enhance their motor response in a variety of ways (breakout 2). The simplest approach is to gradually increase the dose of the dopaminergic agent. In the case of dopamine agonists, there is a rationale for trying higher doses of the agonist than are currently recommended to maximally delay the introduction of levodopa and prevent motor complications. However, there are no data to support this approach, and do-



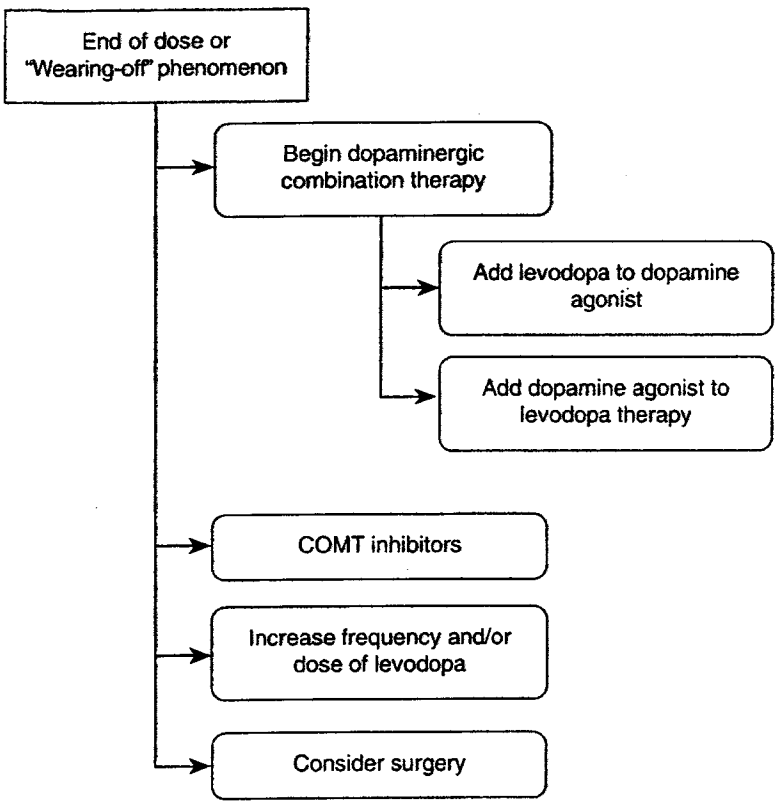
Breakout 2. There are several strategies for approaching patients who experience suboptimal control at the time of peak effect. If they were started on a dopamine agonist or levodopa, the simplest approach is to gradually increase the individual dose. Many clinicians prefer to add a dopamine agonist at this stage because of the decreased risk for motor complications and concerns about levodopa toxicity. If patients were initiated on a dopamine agonist, most clinicians would add levodopa. Therefore, most patients in this group will end up on combined therapy with levodopa and a dopamine agonist. It is wise to introduce either levodopa or a dopamine agonist at a low dose, escalate slowly, and employ the lowest dose that provides a satisfactory clinical response. It may be advantageous to administer levodopa in combination with a COMT inhibitor because of enhanced efficacy and a reduced potential for motor complications. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

pamine agonists at high doses can be associated with neuropsychiatric side effects, sedation, and sleep episodes (see section on Sleep Disorders). For patients receiving levodopa monotherapy, there is growing evidence that levodopa is associated with an increased risk for motor complications[153,154] and that these risks may be increased with higher levodopa doses.[147] An alternate approach is to employ combined therapy with both a dopamine agonist and levodopa. The combination of levodopa and a dopamine agonist can provide improved efficacy in comparison to a dopamine agonist alone and reduced motor complications in comparison to levodopa alone.[153,154,199,217] Therefore, regardless of initial therapy, many patients end up on combined therapy with a dopamine agonist and levodopa. The compelling evidence regarding the capacity of dopamine agonists to delay motor complications associated with levodopa suggests that it is better to initiate therapy with a dopamine agonist and supplement with levodopa when necessary. With either a dopamine agonist or levodopa, it is wise to introduce the dopaminergic therapy in a low dose, escalate slowly, and employ the lowest dose that provides a satisfactory clinical response.

COMT inhibitors are useful adjuncts to levodopa that also may be useful in managing patients with a suboptimal clinical response. As described above, these agents block peripheral levodopa metabolism, thereby enhancing its brain availability. COMT inhibitors reduce "off" time in fluctuating PD patients,[253-257] increase the duration of benefit after a single dose of levodopa,[250] and enhance the motor response and activities of daily living in nonfluctuating patients.[259,260] COMT inhibitors also alter the pharmacokinetics of levodopa so as to provide more stable plasma levels and a theoretically reduced risk for induction of pulsatile stimulation of dopamine receptors and consequent motor complications. Adding a COMT inhibitor to levodopa is therefore an option for patients with suboptimal motor response who are taking levodopa alone or a combination of levodopa with a dopamine agonist. Indeed, an argument can be made for administering levodopa with a COMT inhibitor from the time it is first instituted.[258,266] Studies testing this hypothesis are in the planning stages. See a more complete discussion in the above section on COMT inhibitors.

End-of-dose or "wearing-off" phenomenon. The end-of-dose phenomenon or "wearing-off" effect is said to occur when the duration of benefit after a given dose of levodopa wanes after less than 4 hours. The particular treatment depends on the severity of the wearing-off problem and on how dopaminergic therapy was initially started (breakout 3). Treatment options are similar to those for suboptimal motor response and include the following:

Addition of a dopamine agonist: If the patient is not already receiving a dopamine agonist, its introduction can reduce "off" time in fluctuating



Breakout 3. Patients with "wearing off" of their levodopa effect before the next dose may respond to manipulation of the timing and/or dose of levodopa therapy. The addition or increase in dose of a dopamine agonist also may be helpful. COMT inhibitors as an adjunct to levodopa have been shown to reduce "off" time. Patients who do not respond to the above measures may be candidates for surgical intervention. Efforts should be made in the early stages to utilize a therapeutic strategy that minimizes the likelihood of motor complications. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

patients.[196-205] The dose of levodopa should be maintained until a clinical response to the dopamine agonist is achieved. It then can be gradually lowered as the clinical effects of the dopamine agonist become apparent. In general, it is preferable to use a low dose of levodopa plus a low dose of a dopamine agonist rather than to use high doses of either agent alone. Occasionally, switching from one dopamine agonist to another is helpful, but there are no data supporting the use of multiple dopamine agonists at the same time. As discussed above, it is preferable to initiate agonists before the development of "wearing off" in an attempt to delay the onset of motor fluctuations.

Addition of a COMT inhibitor: As an adjunct to levodopa, COMT inhibitors can significantly reduce "off" time and increase "on" time in patients with "wearing-off" episodes.[250,253-257] These drugs are easy to administer and are generally well tolerated (see above). Patients should be advised that they may develop new-onset or worsening of dyskinesia within 1 or 2 days of adding the COMT inhibitor and that a 15 to 30% reduction in levodopa dose may be required. This is more likely to occur if the patient is already experiencing dyskinesia. In countries in which tolcapone is still available, liver function tests must be strictly monitored and diarrhea may necessitate drug withdrawal in 5 to 10% of patients. Entacapone has not been associated with serious liver dysfunction, and diarrhea is a much milder problem than with tolcapone. For these reasons, entacapone is presently the COMT inhibitor of choice.

Manipulation of the dose of levodopa: Increase the levodopa dose if the patient is not experiencing concomitant dyskinesia, or increase the frequency and use smaller doses if the patient does have dyskinesia. Shortening the interval between levodopa/carbidopa doses is a commonsense strategy for countering "wearing-off" effects. Optimally, the next dose should be given just before the beneficial effects of the previous dose have worn off. This approach is now being employed less frequently because of the risk for motor complications associated with high doses of levodopa.

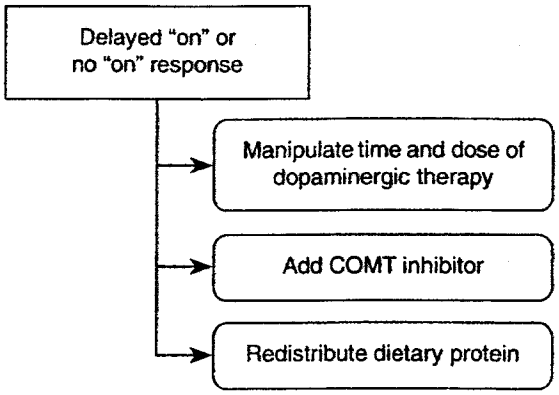
Use of a controlled-release formulation of levodopa (Sinemet CR or Madopar HBS): A long-acting levodopa formulation can be useful in the early stages of the "wearing-off" phenomenon. Substituting controlled-release levodopa/carbidopa for the standard formulation can add 60 to 90 minutes to the response duration after a single-dose administration.[298] The bioavailability of controlled-release formulations of levodopa is less than that of regular levodopa, and a dose increase of 20 to 30% may be required to compensate for this. Long-acting formulations of levodopa are perhaps most valuable in dealing with the wearing-off effects that occur overnight and are best avoided in the later stages of the disease because they may induce prolonged dopaminergic side effects such as dyskinesia and psychosis.

Reduction of total daily dietary proteins or a protein redistribution diet may reduce wearing-off effects in some patients[299] because large, neutral amino acid breakdown products of dietary proteins can compete with levodopa for absorption from the gut and transport into the brain.[194] Patients with advanced disease have reduced striatal dopamine terminals and a decreased capacity to store dopamine. They are therefore increasingly dependent on peripheral levodopa availability for maintaining striatal dopamine levels. Under these conditions, even a minor reduction in levodopa absorption or transport into the brain can lead to a dramatic reduction in striatal dopamine levels and the failure of a given levodopa dose to induce an "on" response. Indeed, measures of ventricular dopamine concentrations in patients with advanced PD indicate that there is a minimal or threshold levodopa level that is necessary for an "on" response to occur.[300] Consuming most of the daily protein requirement during only one meal (often supper) may allow better motor responses to levodopa to be obtained after the other meals of the day. However, the benefits obtained with dietary manipulation are short term, the diet is unpleasant, and a dietitian should be involved to ensure that the minimal daily protein requirements are met. A more practical approach that may be of value in a limited number of patients is simply to administer levodopa on an empty stomach 1 hour before or after each meal.

Subcutaneous (sc) apomorphine can be used as rescue therapy for patients experiencing severe "off" episodes.[301] Unfortunately, it is not approved for routine use in the United States, although regulatory studies have begun. The response to sc apomorphine is rapid and of short duration, with onset of benefit in approximately 3.5–12.5 minutes and loss of benefit after approximately 1 hour. The apomorphine-induced "on" state is comparable to the peak levodopa response, and although the motor response is relatively brief it provides predictable "on" time for the patient in which he or she can complete a chore and during which the next dose of levodopa/carbidopa can take effect. The potential emetic side effect of apomorphine necessitates concomitant use of domperidone, a peripheral dopamine antagonist that does not cross the blood–brain barrier and hence does not exacerbate parkinsonism. Domperidone is not available in the United States but can be obtained in most other countries.

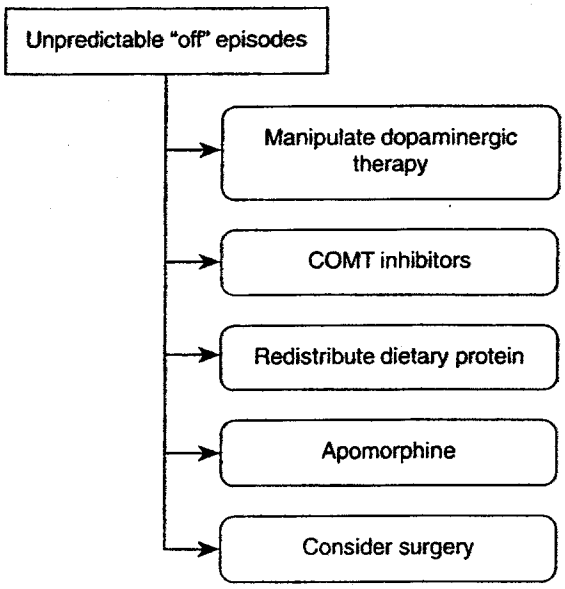
Continuous dopaminergic stimulation: Many studies have demonstrated the capacity of levodopa or dopamine agonists to reduce "off" time when administered continuously around the clock or at least during the waking day.[210,213,302-307] Although these studies have primarily been single-center, open-label studies without controls, they consistently demonstrate reduced "off" time coupled with reduced or at least no worsening in dyskinesia. The basis of these effects is not known. Improvement in "off" responses occur rapidly suggesting that it is a pharmacologic effect, but the reduction in dyskinesia occurs over weeks to months suggesting that this occurs through plastic changes. Levodopa doses do not need to be increased, arguing against tolerance.[209] Although such procedures have the potential to benefit patients with severe motor fluctuations, they are extremely difficult to sustain for both the patient and the physician. Therefore, they are rarely performed outside of research settings.

Patients who do not respond to the above measures and who experience disabling "off" episodes may be candidates for surgical intervention (see below).



Breakout 4. Patients who experience a delayed "on" or no "on" response after a dose of levodopa usually do not accumulate sufficient levodopa in the brain to induce an "on" response. Therapeutic strategies can include increasing the dose of the dopaminergic agent, adding a COMT inhibitor, and redistributing dietary protein. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

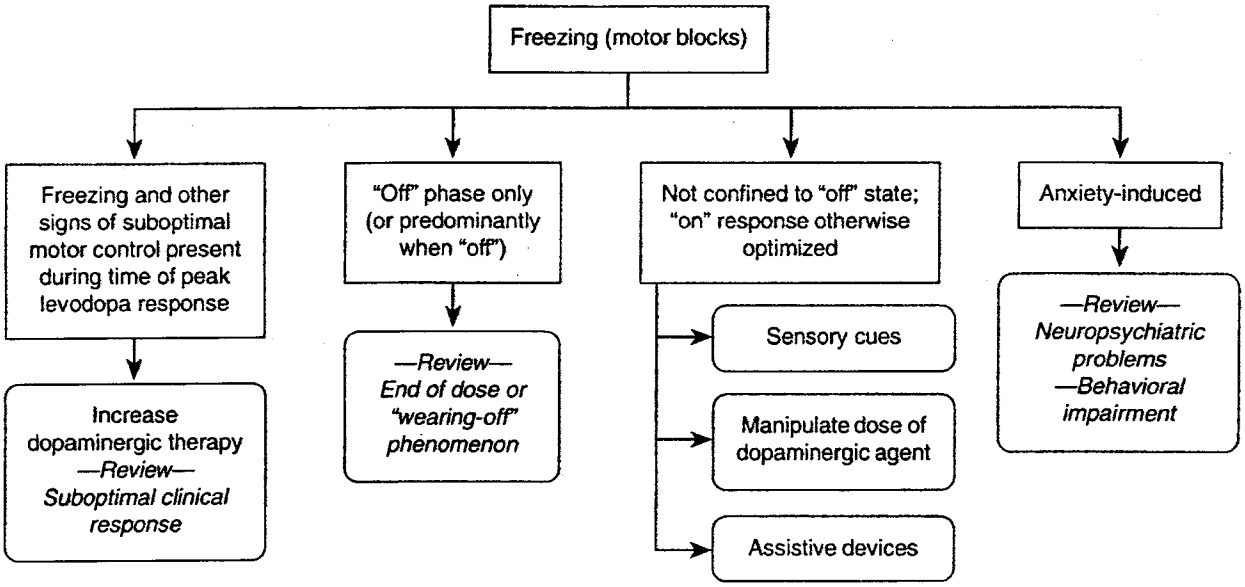
Delayed "on" and no "on" response. In advanced disease, fluctuating patients may occasionally experience a marked delay in responding to a given dose of levodopa or may fail to respond entirely. These phenomena are known as the delayed "on" and no "on" responses, respectively. They generally result from inadequate transport of levodopa to the brain in patients who are totally dependent on the peripheral availability of levodopa. This can be due to an inadequate levodopa dose, slowing of GI transit time, and competition for levodopa absorption by dietary amino acids (breakout 4). An increased dose of levodopa can provide more dopamine to the brain. However, these patients often have advanced disease and a narrow therapeutic window. Therefore, a dose of levodopa sufficient to induce a motor response may also induce severe dyskinesia. The addition of a COMT inhibitor may be helpful by providing more constant brain absorption of levodopa and may permit levo-



Breakout 5. Occasional patients suffer from unpredictable "off" episodes. Dietary protein manipulation may allow better levodopa absorption and permit a motor response after a given dose. Levodopa should be administered 1 hour before or after meals. In extreme cases, all protein can be administered with the evening meal, thereby permitting a response during the rest of the day. COMT inhibitors or adjunctive dopamine agonist therapy may occasionally be beneficial in patients with unpredictable "off" states. Subcutaneously administered apomorphine, if available, can provide rescue therapy for patients who experience an unpredictable "off" state, but it is short-lasting and management-intensive. In general, these patients are difficult to control with any of the available medications and therefore they are often considered for a surgical procedure. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

dopa titration to find a dose that provides benefit without dyskinesia. No "on" or delayed "on" episodes often occur after high-protein meals. Taking levodopa on an empty stomach or reducing the protein concentration in the meal may permit the same dose of levodopa to induce an "on" response. Finally, levodopa is absorbed in the small bowel and not in the stomach. Many PD patients suffer a slowing of GI transit time so that delivery of levodopa to the stomach is delayed and sufficient concentrations to provide an "on" response are not present at a given time. Agents that enhance bowel motility, such as domperidone or cisapride, may be helpful in this situation, although cisapride has recently been withdrawn in the United States because of its potential for cardiac toxicity.

Unpredictable "off" episodes. Most levodopa-treated PD patients with motor fluctuations experience predictable "off" periods that occur when the beneficial effect of a given dose of levodopa wears off (see above). Occasionally, patients may suffer from "off" episodes that are unpredictable and that occur suddenly and without warning. Patients may convert from an "on" to an "off" state in seconds or minutes. In these cases, the "off" periods seemingly have no relationship to the time of levodopa administration or to the plasma levodopa concentration. These complications tend to occur in patients with advanced disease and are often accompanied by severe dyskinesias during the "on" stage. Patients may be profoundly akinetic during the "off" episode and markedly dyskinetic when "on." The basis of this phenomenon is not known. Many of the sudden "offs" are probably pharmacokinetically based and occur in



Breakout 6. Attention to the timing of freezing in the dopaminergic therapy response cycle determines the treatment strategy. Freezing, in conjunction with other prominent signs of parkinsonism during the time of peak levodopa effect, suggests an underdosed state. Patients whose freezing is confined to the levodopa "off" states are often responsive to more aggressive medical treatment. In contrast, drug reduction is less likely to help patients with "on"-period freezing and could lead to acute deterioration in parkinsonism. However, occasionally it may be helpful. Sensory and motor cues often are useful. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

patients with advanced PD and minimal capacity to centrally store levodopa. They are therefore particularly vulnerable to even minimal fluctuations in peripheral levodopa availability. However it may be that pharmacodynamic mechanisms also play a role. The treatment approach is similar to that described above for "wearing-off" episodes, but unpredictable "off" episodes are usually much more difficult to treat (breakout 5). It is important to take a good history and, if possible, to observe the patient through a series of dosing cycles so as to define the nature of the levodopa response and the possibility that these episodes are occurring on a pharmacokinetic basis. In many instances, these motor complications cannot be controlled with any of the conventional medical strategies, and it may be necessary to consider continuous dopaminergic stimulation or surgical therapy. For these reasons, all efforts should be made in the early stages of the disease to initiate treatment in such a way as to minimize the likelihood that such motor complications will develop.

Freezing (motor blocks). Transient hesitancy or freezing of motor behavior can occur with any movement, but it is most apparent and troublesome to PD patients when it involves gait. This frequently occurs on initiating gait (start hesitation) or when passing through a tight space such as a doorway. Freezing can be a manifestation of either an inadequate or an excessive dopaminergic effect. In most, it appears to be independent of medication and is refractory to manipulation of levodopa.

Attention to the timing of freezing in the levodopa response cycle determines the treatment strategy (breakout 6). Freezing, in conjunction with other prominent signs of parkinsonism during the time of the peak levodopa effect, suggests an underdosed state that may respond to larger individual doses of levodopa/carbidopa or other dopaminergic strategies (see subsection on Suboptimal Clinical Response and section on Motor Fluctuations; breakout 2). Occasional patients improve with increased levodopa dosages, even if other signs of parkinsonism appear to be optimally controlled. Hence, a brief trial of an incremental increase in levodopa dosing may be indicated. Although "off"-period freezing may not respond as consistently to dopaminergic therapy as other parkinsonian motor manifestations, it can occasionally be helped with these drugs. Patients with "on"-period freezing or those who experience freezing despite maximal medical treatment are more difficult to manage. A reduction in the dosage of levodopa, dopamine agonists, or selegiline may be helpful for "on"-period dyskinesia, but this may lead to worsening of other parkinsonian features. In the majority of patients, drug manipulation is not effective, and it has been postulated that freezing may be a nondopaminergic phenomenon. Regardless of cause, gait freezing and similar motor blocks often can be helped by certain nonpharmacologic techniques that involve the use of sensory or mental imagery, cues, or devices.[308] Some approaches that have been used to try and counter freezing episodes include the following:

Stepping toward a target on the ground;

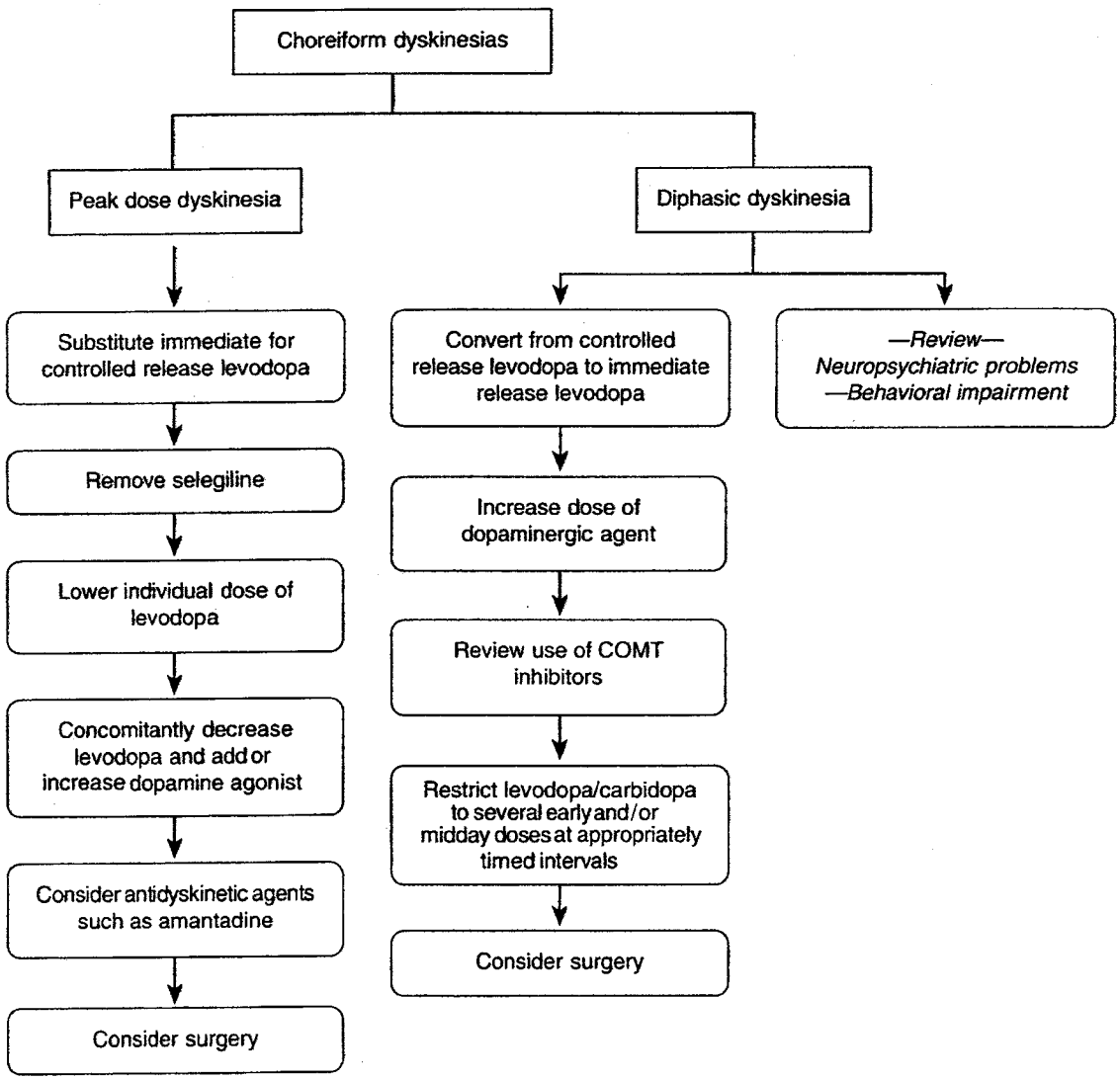
stepping over a cane laid on the floor in front of the foot;

taking the first step with a stiff leg in a military manner; and

counting out a rhythm or singing and then trying to walk in concert with the rhythm.

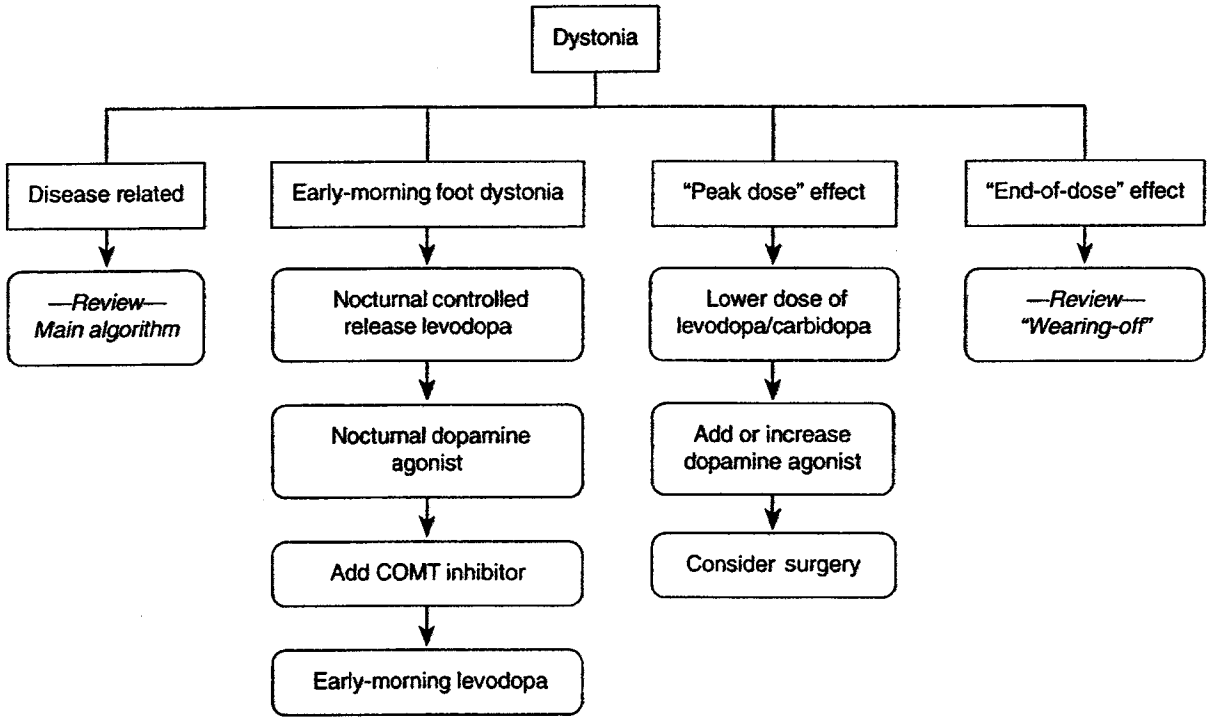
The general idea is to substitute a conscious motor program for the malfunctioning automatic motor program. After experimenting with different ploys, patients typically find at least one strategy that is helpful. Anxiety can exacerbate the tendency for motor blocks/freezing. If this is a major factor, measures aimed directly at treating the anxiety state may be appropriate (see subsection on Behavioral Impairment or Mood Disturbance in section on Neuropsychiatric Problems).

Dyskinesias Peak-dose dyskinesia. Peak-dose dyskinesias occur at the time of maximal levodopa benefit and plasma levodopa concentration and frequently develop in conjunction with motor fluctuations. Like motor fluctuations, they are believed to be related to plastic changes and abnormal neuronal firing patterns that develop in response to pulsatile stimulation of the denervated dopamine receptor.[170] Treatment options are illustrated in breakout 7. In the earliest stages, dyskinesias usually are not troublesome to the patient and can be readily controlled by small reductions in levodopa dosage. If the patient is receiving only levodopa, addition of a dopamine agonist coupled with a reduction in the levodopa dose may reduce dyskinesia and provide a more sustained motor benefit. Dopamine agonists may be particularly valuable when the dyskinesia has a dystonic quality. COMT inhibitors are primarily recommended for patients with isolated motor fluctuations, but they also may be of value in managing patients who also have dyskinesia. The addition of a COMT inhibitor may permit a reduction in levodopa dose and may help determine a levodopa dosing level that provides antiparkinsonian benefits without dyskinesia. It is important in this context to recall that the introduction of a COMT inhibitor to a dyskinetic patient often causes an initial worsening of dyskinesia, and levodopa dose reductions will probably be required. In general, it is difficult to determine a levodopa dose that provides motor benefit but does not induce dyskinesia, particularly with oral tablets. If patients are particularly sensitive to levodopa, liquid levodopa/carbidopa may enable more sensitive titration. Unfortunately, liquid levodopa is not commercially available and must be made fresh each day. This is a problem for many PD patients. It is best to avoid controlled-release formulations of levodopa in dyskinetic patients because they are long-acting and can be associated with prolonged bouts of dyskinesia.



Breakout 7. Dyskinesia can be of the peak-dose or D–I–D (dyskinesia–improvement–dyskinesia) type. The strategy for managing peak-dose dyskinesia response is to lower the individual doses of levodopa in 25-mg increments. If this results in a relative "off" state, a dopamine agonist should be introduced or the dose increased. It is usually easier to manage dyskinetic patients if they are switched from controlled-release to immediate-release levodopa and selegiline is discontinued. If a COMT inhibitor has been recently introduced, a 20–30% reduction in levodopa dose is usually helpful. Patients who are extremely sensitive to levodopa may benefit from close titration with liquid levodopa/carbidopa. Antidyskinetic agents (such as amantadine) or surgery should be considered in refractory patients. D–I–D dyskinesia can be more difficult to manage. Trials of higher or more frequent doses of the dopaminergic agent may be helpful. Four or five overlapping doses may provide benefit for occasional patients. Surgery is an option for patients with troublesome dyskinesia who cannot be adequately controlled with medical management. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

With advancing disease, dyskinesia can become very severe and represent a major source of disability to the patient. In this situation, patients often have a narrow therapeutic window such that even a small reduction in the levodopa dose aimed at controlling dyskinesia can result in a dose that is insufficient to induce an "on" response, and a dose that induces an "on" response causes dyskinesia. In this circumstance, patients can cycle between "on" responses that are complicated by disabling dyskinesia and "off" responses in which they suffer severe motor impairment. Some physicians have had success in managing this type of patient with very high doses of dopamine agonists coupled with a 75 to 90% reduction in levodopa dose.[208] This strategy may be helpful for individual patients but it is associated with a high incidence of side effects and is rarely indicated in routine practice. Continuous dopaminergic stimulation can either improve or worsen dyskinesia[209] and is not a practical solution for most patients. Proof of principle studies have, however, demonstrated the capacity of continuous infusion of dopamine agonists or levodopa to improve both dyskinesia and motor fluctuations.[209] Attempts to repro-



Breakout 8. Dystonia is a common problem in PD and may occur as part of the disease or secondary to levodopa therapy. A careful history to define the type of dystonia is of fundamental importance. For dystonia that occurs in the untreated patient or at the end of a levodopa response cycle, the usual dopaminergic strategies for improving motor control are appropriate. Dopamine agonists are particularly effective. For symptoms of painful dystonia on awakening, a bedtime dose of controlled-release levodopa or a dopamine agonist can be helpful. COMT inhibitors also may be a useful addition. Dystonia secondary to dopaminergic medication is treated similarly to peak-dose dyskinesia (see breakout 7). Treatment usually consists of a reduction in levodopa dose coupled with an addition or increase in the dose of a dopamine agonist. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

duce these results with oral doses of dopaminergic agents are currently underway. A number of other drugs are also being investigated to assess their potential to provide antidyskinetic effects. NMDA receptor antagonists such as amantadine have been shown to reduce dyskinesias in MPTP-treated monkeys and PD patients,[293-295] although they may be associated with cognitive side effects. Atypical neuroleptics and a variety of agents that act on nondopaminergic components of the basal ganglia are also being investigated and are discussed in more detail below (see section on Future Directions). Patients with severe dyskinesia that cannot be adequately regulated with any of these approaches may be candidates for surgical treatment (see below). Again, it should be emphasized that motor complications such as dyskinesia may be extremely difficult to control once they develop, and all efforts should be made to prevent their development in the first place (see section on Pharmacologic Approach to Patients with Early PD).

Diphasic (D–I–D) dyskinesia. A second pattern of dyskinesia is known as diphasic or dyskinesia–improvement–dyskinesia (D–I–D) dyskinesia.[141] Here, adventitious dyskinetic movements occur at the beginning and at the end of the levodopa response cycle but not during the drug's peak effect. Patients experience dyskinesia as they turn "on," have no dyskinesia at the time of the peak levodopa dose and clinical benefit, and experience dyskinesia again when they begin to turn "off." This pattern usually occurs in patients with advanced disease who have previously experienced peak-dose dyskinesia. D–I–D dyskinesias tend to be choreiform, to be stereotypic, and to involve the lower extremity. The period of dyskinesia when the patient is turning "off" is typically more prolonged and troublesome than the dyskinetic period when the patient is turning "on." Occasionally, patients with D–I–D dyskinesia experience dyskinesia in the leg at the same time as parkinsonian features in the other extremities.

The D–I–D pattern is much less common than peak-dose dyskinesia and can be difficult to diagnose because it may not be obvious to either the patient or the clinician. It also can be very difficult to treat (see breakout 7). When D–I–D first begins to appear, patients may respond to simple measures, such as more frequent or higher doses of levodopa/carbidopa. This may provide a more continuous "on" state and prevent the patient from cycling through the dyskinetic phases. One treatment strategy is to overlap multiple doses of levodopa/carbidopa at intervals that are just long enough to preclude the development of the dyskinetic phase at the end of each dosage cycle. Although administration of levodopa/carbidopa doses at short intervals can successfully

prevent the end-of-dose dyskinetic period for a while, this strategy tends to fail after approximately four or five overlapping doses. At this point, patients begin to note a decreasing threshold for dyskinesias and an inability to suppress them despite larger and larger doses of levodopa/carbidopa. They can, however, time their cycle so that it is more predictable, and they can arrange to be at home during the time when the dyskinesia is expected. Once they have completed the dyskinetic period, patients typically experience adequate control of their parkinsonian motor symptoms for the remainder of the day, although control is not quite as good as during the time of peak levodopa response. This control typically continues overnight and into the next morning. If left untreated, patients usually start to experience increasing motor manifestations of parkinsonism by mid- to late morning, at which time they can restart their levodopa cycle. With this strategy, some patients can achieve good control of parkinsonian symptoms during the midday and adequate control during other portions of the day. The timing of doses for D-I-D patients should be based on the levodopa/carbidopa response duration in an individual patient.

As with peak-dose dyskinesia, it is usually easier to control dyskinesia by switching from the controlled-release to the regular formulation of levodopa/carbidopa. Indeed, controlled-release levodopa or COMT inhibitors may actually worsen D-I-D dyskinesia because of its tendency to be associated with relatively low plasma concentrations of levodopa, which predispose to this complication. Therefore, they are not recommended in this situation. Addition of a dopamine agonist or liquid levodopa/carbidopa can be tried but is usually not helpful for D-I-D dyskinesia. Subcutaneous apomorphine may provide additional "on" time to sustain the patient until a response is achieved from the next dose of levodopa/carbidopa. Patients who do not achieve acceptable relief from these medication adjustments may be candidates for surgery.

Regardless of the type or pattern of dyskinesias, they can be unmasked or worsened by anxiety-provoking situations. If this is a problem, interventions directed at treating underlying neuropsychiatric issues may be appropriate (see section on Neuropsychiatric Problems).

Dystonia. Dystonia may occur in relation to levodopa or to the parkinsonism itself. It is important to take a careful history, noting the relationship between the timing of the emergence of dystonia and the timing of levodopa administration. Painful dystonic cramping of the toes and feet on awakening is a common complaint in untreated PD patients and in patients in whom the morning dose of levodopa has not yet taken effect. Some patients also may experience painful or uncomfortable dystonia at the end of their levodopa response cycle. In these cases, the usual strategies for improving PD motor control are warranted (breakout 8). Additional options aimed at managing early morning dystonia include administration of a bedtime dose of controlled-release levodopa/carbidopa or a long-acting dopamine agonist. Patients can also try taking a dose of levodopa/carbidopa before they are scheduled to arise, but this requires the patient to remain in bed after awakening. Other agents that can be considered include anticholinergic drugs and botulinum toxin injections, but these are rarely of practical value.

Dystonia also may represent a form of dyskinesia and may occur secondary to levodopa therapy. In fact, dystonia is frequently the earliest manifestation of dyskinesia. Strategies designed to prevent the development of motor complications may prevent the development of levodopa-induced dystonia. Once peak-dose dystonia occurs, therapy is similar to that described for peak-dose dyskinesia (see above; and see breakout 7). A reduction in the size of the individual dose of levodopa/carbidopa may reduce dystonia but may cause deterioration in PD signs and symptoms. Dopamine agonists are particularly helpful in controlling levodopa-induced dystonia and can be employed as an adjunct to levodopa coupled with a reduction in levodopa dose. If all other measures fail and dystonia is disabling, patients can be considered for a surgical procedure.

Table 7 *Surgical procedures for PD*

Ablative procedures
Thalamotomy
Pallidotomy
Subthalamotomy
Stimulation procedures
Thalamus (Vim nucleus)
GPi
STN
Restorative procedures
Fetal human nigral transplantation
Fetal porcine nigral transplantation
Trophic factors (e.g., GDNF)

SURGICAL MANAGEMENT OF PD

The potential of surgical therapies to provide benefit for PD patients who can no longer be satisfactorily controlled with available medical therapies is a major advance in modern therapy. Over the past century a number of surgical treatments have been employed in PD.[309-311] Historically, lesions of the corticospinal motor tracts have been noted to improve parkinsonian features (especially tremor) but only at the expense of voluntary motor paresis, and these techniques have been abandoned. In the 1940s, lesions of the ansa lenticularis and globus pallidus were noted to provide benefit to PD patients without inducing paralysis, and pallidotomies began to be performed routinely.[312,313] However, adverse events were a concern because of the proximity of the globus

Figure 17. DBS system. An electrode is implanted in the target region in the brain and connected to a pulse generator that is placed subcutaneously over the chest wall. Provided courtesy of Medtonic, Inc.

pallidus to the internal capsule and the optic radiation. Furthermore, bilateral lesions were associated with additional risks for dysphagia, dysarthria, and cognitive impairment.[314] In the 1950s, Cooper[315] accidentally ligated the anterior choroidal artery with resultant infarction in the thalamus, and noted improvement in PD tremor. Because of improved results and reduced side effects, thalamotomy replaced pallidotomy as the preferred treatment for PD tremor. However, with the introduction of levodopa in the late 1960s, surgical procedures were largely abandoned.

In recent years there has been a resurgence of interest in surgical procedures for the treatment of patients with advanced PD, based on: (a) the limitations of levodopa therapy; (b) advances in the ability to safely perform stereotactic neurosurgical procedures; (c) advances in neuroimaging and single-cell recording techniques that permit more accurate target localization and reduced risk of adverse effects; (d) new insights into the organization of the basal ganglia that provide a rational basis for targeting specific brain regions[155,156,159]; (e) studies observing that pallidotomy benefits are most pronounced when lesions are made in the posteroventral portion of the GPi[316]; (f) the development of high-frequency deep brain stimulation (DBS) procedures that simulate the effects of ablative procedures but do not necessitate making a destructive brain lesion[317]; and (g) the determination that transplanted dopaminergic cells can survive and reverse motor disabilities in animal models of PD and the demonstration that transplantation procedures in PD patients are feasible.[318,319] Surgical therapies that are currently being employed or that are under active investigation in PD are listed in table 7.

Targets for surgical procedures and the underlying rationale for choosing them are as follows:

Ventral intermediate nucleus of the thalamus (Vim nucleus): Ablative and stimulation procedures are employed primarily to treat tremor, based on evidence that lesions in the thalamus provide a potent antitremor effect in PD and that lesions in the Vim nucleus provide the most dramatic anti-tremor effects.[320-322]

Globus pallidus pars interna (GPi) and subthalamic nucleus (STN): Physiologic and metabolic evidence indicates that both the GPi and the STN are overactive in PD[34,155,156,159,323,324] and that lesions of these structures provide antiparkinsonian effects in animal models of PD as well as in PD patients.[163,164,167,325-327] Ablation and stimulation procedures are now being performed in each of these targets in an attempt to inhibit abnormal neuronal firing patterns, and to prevent basal ganglia output neurons from providing misinformation to thalamic and cortical motor regions. Preliminary results note benefits in PD patients with respect to akinesia, rigidity, gait, postural disturbances, and drug-induced dyskinesias, in addition to tremor.

Striatum (especially the posterior putamen): The striatum is the major target of the nigral dopaminergic neurons and projections that degenerate in PD and is the major site of dopamine loss in this condition. It (and particularly the postcommissural portion of the putamen) is therefore a rational target site for transplantation strategies utilizing embryonic dopaminergic neurons or trophic factors.[319]

Surgical therapies historically have utilized ablative procedures (e.g., chemical, radio frequency, thermal) to make a destructive lesion in overactive or abnormally firing brain targets. However, ablative procedures are associated with the risk of damage to neighboring structures with consequent neurologic dysfunction.[314] This is a particular problem with bilateral procedures for which there are the additional risks of cognitive, speech, and swallowing impairment. There are also specific problems with respect to lesions of the STN, which are associated with the risk of a potentially fatal hemiballismus.[328] As a result, many physicians are reluctant to perform bilateral surgical procedures or even a unilateral subthalamotomy in PD patients, even though PD is a bilateral disease. This has led to the introduction of high-frequency DBS procedures in PD. DBS is a surgical treatment that has long been used in the treatment of pain. It is based on observations indicating that high-frequency stimulation of specific brain targets can induce functional benefits that simulate the effects of a destructive lesion without the need for making a destructive brain lesion.[317] DBS is accom-

***Therapeutic Breakout 7** Thalamotomy*

Advantages
Consistent and long-lasting improvement in contralateral tremor
May improve contralateral dyskinesia
Widely available; many surgeons have experience with the procedure
Disadvantages
Necessitates needle passage(s) through the brain
No meaningful effect on the more disabling parkinsonian features (e.g., bradykinesia and gait dysfunction)
Necessitates making a lesion in the thalamus
Bilateral lesions associated with risk for severe dysarthria, dysphagia, and cognitive dysfunction

plished by implanting an electrode with four contacts into a target site within the brain and connecting it to a pulse generator placed subcutaneously over the chest wall (figure 17). The stimulator settings can then be adjusted with respect to electrode configuration, voltage, frequency, and pulse width to maximize benefit and minimize side effects. The precise mechanism of action of DBS remains to be defined. Possible mechanisms include depolarization blockade, release of inhibitory neurotransmitters, jamming of abnormal neuronal firing patterns, and backfiring with activation of inhibitory neurons in other structures. Through whatever mechanism, DBS can induce clinical benefits that mirror those obtained with destructive lesions. DBS offers the following advantages in comparison to ablative procedures:[329] (a) it does not require making a destructive lesion in the brain; (b) it can be performed bilaterally with relative safety; (c) stimulation parameters can be readjusted postoperatively to try to improve efficacy or decrease adversity; and (d) it does not preclude the use of future therapies that might require preservation of the integrity of the basal ganglia to be effective.

Side effects of the DBS procedure can be related to the surgical procedure, the device, or stimulation. The procedure requires a needle to be passed through the brain, carrying with it the risk for hemorrhage and damage to neighboring brain structures, but the risks are less than those seen with ablative procedures, particularly when they must be performed bilaterally.[314,330] Complications associated with the device are related to mechanical (e.g., lead fracture, movement of the electrode, skin erosion) or infectious problems and may ultimately require lead reimplantation. Side effects related to stimulation are common but transient and can readily be controlled by adjusting the stimulation variables or by turning off the stimulator. Stimulation variables include the electrode configuration, voltage, frequency, and pulse width and therefore effectively offer an infinite variety of stimulation settings. This can be a problem because of the length of time and number of visits that may be required to determine the optimal stimulation settings. This is a practical problem because it may be difficult to select the optimal setting from among so many, and the complexity of this analysis may limit the utility of this procedure. Recent reports of a standard method for determining the optimal stimulation settings that can be accomplished in a single visit may help to obviate these problems.[331] Finally, the battery must be replaced in 1 to 5 years, depending on the stimulation settings chosen, and this requires another surgical procedure. DBS is approved for use in the United States for the

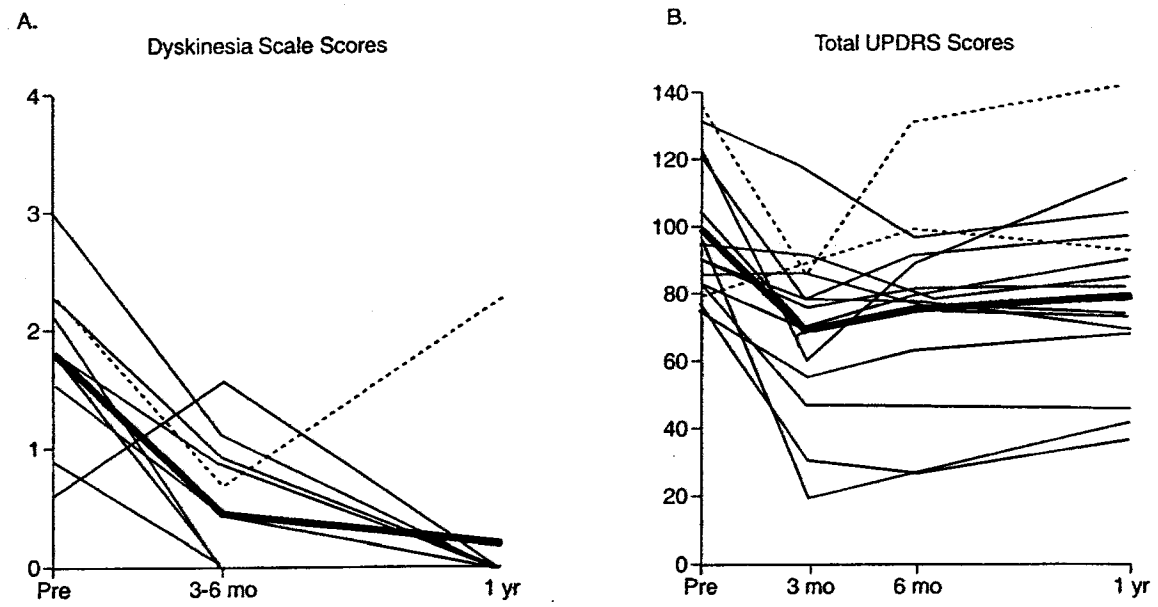


Figure 18. Measures of dyskinesia (A) and UPDRS (B) at baseline and at periodic intervals after unilateral pallidotomy. Contralateral dyskinesia is dramatically improved in almost all patients. There is also an improvement in the UPDRS score, although the benefit is less striking. (Reproduced with permission from Baron et al.[163])

Vim nucleus target, and application is pending for GPi and STN targets. All of these targets are approved for use in Europe and in many other countries.

The clinical results of the different surgical procedures in PD patients are described below.

Ablative procedures

Thalamotomy. Thalamotomy was extensively performed as a treatment for PD tremor in the prelevodopa era.[320,321,330,332,333] Although most of these studies were anecdotal, they indicate that thalamotomy consistently provides improvement in contralateral tremor and rigidity. More modern studies similarly have observed that thalamotomy is associated with long-lasting tremor reduction in more than 90% of patients.[334-337] Thalamotomy is less effective for rigidity and does not improve other parkinsonian features, such as bradykinesia and gait dysfunction. There are some reports indicating that thalamotomy can provide an antidyskinetic effect in some patients[330]; this appears to be associated with lesions slightly anterior and ventral to the Vim nucleus.

The basis for the antitremor effect provided by thalamotomy is not known but may be due to destruction of autonomously firing tremor synchronous neurons (i.e., neurons that fire at the same frequency as the tremor). Small lesions in the Vim nucleus targeting tremor synchronous neurons are uniformly effective in relieving parkinsonian tremor.[338] The Vim nucleus receives input from two major pathways: pallidofugal fibers that arise from the GPi and cerebellothalamic fibers that arise from the cerebellum. The Vim nucleus, in turn, projects to the motor cortex. As a result of its central connections with motor regions, the Vim nucleus could become passively entrained by oscillations originating in other sites and could, in turn, promote abnormal oscillations throughout the motor system. Therefore, lesions in the Vim nucleus might reduce tremor by curtailing this entrainment even though this may not be the site of origin of abnormally firing neurons. Whatever the mechanism, it is noteworthy that thalamic lesions, which are so effective in ameliorating tremor, have little effect on other parkinsonian features. This suggests that in some way the brain regions that underlie the different motor features of PD are anatomically disparate.

The mortality rate for thalamotomy in PD is less than 0.3% and is usually the result of hemorrhage or postoperative complications, such as pulmonary embolism or infection. Other adverse events can include somnolence, confusion, hemiparesis, limb ataxia, seizures, dysarthria, and aphasia.[313,329] Complications are more common after bilateral thalamotomy, and more than 25% of patients experience postoperative speech, swallowing, or cognitive impairment. Thalamotomy is now rarely performed because of the wider array of antiparkinsonian benefits that can be attained by targeting the STN or GPi and because of the advent of stimulation procedures that avoid the need to make a destructive lesion. The advantages and disadvantages of thalamotomy are provided in therapeutic breakout 7.

***Therapeutic Breakout 8** GPi pallidotomy*

Advantages
Consistent and dramatic improvement in contralateral dyskinesia
Mild improvement in parkinsonian features
Widely available
Disadvantages
Necessitates needle passage(s) through the brain, with risk for hemorrhage
Necessitates making a lesion in the brain with risk for damage to internal capsule and visual pathways
Bilateral lesions associated with additional risks that include cognitive dysfunction, dysphagia, and dysarthria
Optimal target site not precisely defined
Necessity for microelectrode recordings not definitively established
Mechanism responsible for clinical benefit not defined
Lesion may preclude use of more effective therapy in the future

Pallidotomy. Pallidotomy largely disappeared from use as a surgical treatment for PD after the advent of levodopa. The recent resurgence of interest in this procedure is based on evidence that the GPi is overactive in PD[153,154,322-324] and that glutamate antagonists injected into the GPi improve parkinsonism in animal models.[326] Physiologic studies have demonstrated that the sensorimotor region of the GPi is located in its posteroventral portion[331] and that lesions placed in this region provide maximal antiparkinsonian benefit in PD patients.[316,339,340]

The most striking effect of pallidotomy in PD patients is a consistent and dramatic amelioration of contralateral dyskinesia[163,164,341-347] (figure 18). Antidyskinetic benefits are observed in approximately 90% of patients, with mean improvements of 1 or 2 points on the UPDRS dyskinesia score and 50 to 60% in the dyskinesia rating scale. Improvement in motor function can also be observed, but this is less dramatic and less consistent. The total UPDRS motor score has been reported to be improved by 18 to 46% after pallidotomy, and significant benefits have been observed in contralateral tremor, rigidity, and bradykinesia. Benefits with respect to dyskinesia and, to a lesser extent, motor benefits have been shown to persist through 5 years of follow-up.[348] However, in another study, only dyskinesia and tremor remained improved after 3 years of follow-up,[349] even though more widespread motor benefits had been observed at 6 months.[346] These authors concluded that improvement in dyskinesia was the only long-term benefit of pallidotomy.

In assessing the results of pallidotomy, it should be appreciated that these studies have all been open-label trials and did not control for placebo effect or physician bias. One prospective, single-blind, multi-

Therapeutic Breakout 9 *Deep brain stimulation procedures*

Advantages
Do not necessitate making a destructive brain lesion
Bilateral procedures can be performed with relatively minimal risk
Potential to stimulate brain targets one might be hesitant to lesion (e.g., bilateral targets, STN, supplementary motor area)
Stimulation settings can be adjusted at any time to maximize benefit and minimize adverse effects
Stimulation of STN and GPi benefit all cardinal features of PD
Do not preclude future therapies that depend on the integrity of the basal ganglia
Disadvantages
Necessitate needle passage(s) through the brain, with risk for side effects
Mechanical and infectious side effects associated with an implanted device
Need to periodically replace battery
Optimal target site not known
Mechanism of action not known
High costs

center 6-month study has been performed. Thirty-seven patients with advanced PD were randomized to receive unilateral pallidotomy or best medical treatment.[350] Significant benefits were noted in the pallidotomy group with respect to UPDRS motor and ADL scores during the "off" stage, for dyskinesia, and for quality of life. These were superior to what was found in the medical group. Benefits with pallidotomy were not observed in motor function during the "on" stage.

It therefore appears that pallidotomy is associated with improvement in contralateral motor features. However, improvement in motor function may reflect, at least in part, improvement in parkinsonian features caused by an increase in the levodopa dose that has been enabled by the reduction in dyskinesia rather than by a direct effect of pallidotomy on motor function. There is some controversy as to whether or not it is necessary to employ microelectrode recordings in performing these procedures. Some have argued that it is necessary for target localization to maximize benefit and minimize the risk for adverse events.[351] Others have argued that utilizing microelectrode recordings increases the number of electrode passes and the risk for an adverse event, and that comparable results can be obtained without the use of this technique.[346]

Serious complications of pallidotomy include contralateral motor deficits, visual field cuts, dysarthria, dysphagia, cognitive changes, and behavioral impairment. The complications of bilateral pallidotomy are more pronounced and include speech difficulties, dysphagia, and cognitive difficulties. Therefore, bilateral operations are not routinely recommended. The advantages and disadvantages of GPi pallidotomy are provided in therapeutic breakout 8.

Subthalamotomy. STN is a rational target in PD because (a) it plays a central role in the organization of the basal ganglia, providing excitatory innervation to both segments of the globus pallidus (GP), the SNr, pedunculopontine nucleus (PPN), and SNc,[352,353] (b) the STN is overactive in PD[160,354] and therefore could account for parkinsonian features according to the classic model, and (c) lesions of the STN improve motor function in the MPTP-treated monkey.[325,326] Furthermore, it has been hypothesized that lesions of the STN might block STN-mediated excitotoxic damage in its target neurons and thus provide a neuroprotective effect.[93] Lesions of the STN have been shown to protect SNc neurons from 6-OHDA-induced toxicity.[355] However, lesions of the STN cause hyperkinesias and even hemiballismus in normal individuals.[328] Therefore, physicians have been reluctant to lesion this target, even unilaterally. With the introduction of DBS techniques, the benefits of functionally inhibiting this target in PD patients have been demonstrated, and hemiballismus has not been a problem (see below). This has raised interest in the possibility that STN ablative lesions can be safely performed.

Preliminary reports in a small number of PD patients who have undergone either unilateral or bilateral STN lesions indicate that this procedure can provide substantial efficacy without inducing hemiballismus.[167,356] Transient dyskinesia may be seen after surgery but it disappears concomitant with a reduction in antiparkinsonian medication. Clearly, further investigation of this procedure must be performed to determine its safety and efficacy. If it is shown to be effective and well tolerated, it would have the advantage of avoiding the costs and risks associated with DBS while at the same time being potentially better tolerated than other ablative procedures because of the small size of the lesion required.

Deep brain stimulation

DBS of the thalamus (Vim nucleus). DBS of the thalamus was first employed in PD patients who had previously undergone a unilateral thalamotomy to avoid the necessity for bilateral ablative procedures.[317] Subsequent studies have demonstrated that DBS of the Vim nucleus can be used as first-line therapy to ameliorate PD tremor and simulate the effect of thalamotomy without the need to make a lesion. Benabid et al.[357] reported marked improvement in contralateral tremor in 83% of 80 patients treated with thalamic DBS. Koller et al.[358] similarly reported a 71% improvement in contralateral tremor in 24 PD patients after 1 year of Vim nucleus stimulation. Benefits in this study were confirmed in a double-blind crossover evaluation. Patients undergoing DBS of the Vim nucleus did not experience benefit with respect to rigidity, bradykinesia, or gait. Consequently, there was no functional improvement

despite the marked reduction in tremor. Similar results have been observed in other studies.[359,360] Benefits are long-lasting, with tremor amelioration persisting for more than 7 years.[361] Even after this prolonged period of time, when the stimulator is turned off the tremor returns within seconds. This suggests that DBS of the Vim nucleus does not influence the underlying mechanism responsible for tremor. Because tremor is the sole parkinsonian symptom that is affected by DBS of the Vim nucleus, activities of daily living and quality-of-life measures are not improved, as is the case with thalamotomy.

One double-blind study has been performed in 45 PD patients with drug-resistant tremor.[362] Patients were randomized to receive thalamotomy or thalamic DBS for the treatment of PD tremor. The primary outcome measure was the change in functional abilities 6 months after surgery, as measured by the Frenchay Activities Index score. Tremor was either completely or almost completely suppressed in more than 70% of patients in both treatment groups. However, functional improvement, reflecting the combination of both clinical benefit and side effects, was significantly better in patients who received thalamic stimulation. The advantages and disadvantages of DBS procedures are provided in therapeutic breakout 9.

DBS of the globus pallidus (GPi). Stimulation of the GPi was attempted based on the success of thalamic stimulation in the treatment of tremor and of pallidotomy in providing or permitting more widespread improvement in parkinsonian symptoms. In general, DBS of the GPi mimics the beneficial effects of pallidotomy. Several small open-label studies have reported improvement in motor scores, "on-off" fluctuations, and dyskinesias after bilateral and, to a lesser degree, unilateral pallidal stimulation.[363-369] In comparison to the "off-medication" state at baseline, total UPDRS motor scores in the "off-medication" state were increased by 35 to 45% with stimulation. These benefits persisted during 3 to 12 months of follow-up. Similar benefits were noted with respect to ADL scores in the "off" state. DBS–GPi was associated with a marked decrease in levodopa-induced dyskinesias, similar to what has been seen with pallidotomy. This resulted in improved ADL scores during "on" stages as well. The benefits observed were comparable to those seen with pallidotomy.[365]

The results of a 6-month multicenter trial of bilateral DBS–GPi in 38 patients with advanced PD have recently been reported to the United States Food and Drug Administration (FDA).[370] The study included a double-blind crossover evaluation. In comparison to baseline, pallidal stimulation provided improvement in the UPDRS motor score during the "off-medication" state ($p<0.001$) and, to a lesser degree, during the "on-medication" state ($p=0.003$). Pallidal stimulation in the "off-medication" state provided benefits with respect to activities of daily living and each of the cardinal features of PD. These benefits were confirmed in the double-blind crossover evaluation in which UPDRS motor scores were improved by 37% when the stimulator was randomized to be turned on versus when it was randomized to be turned off ($p<0.001$). Dyskinesia scores were significantly improved ($p<0.01$). Home diary assessments showed that "on" time without dyskinesia increased from 28 to 64% of the waking day ($p<0.001$) and "off" time was reduced from 37% to 24% of the day ($p=0.01$). Physician and patient global estimates of severe disability improved from 76 and 82% at baseline to 11 and 14% at 6 months. There was no significant change in the mean daily dose of levodopa equivalents (1,091 ± 543 mg at baseline versus 1,120 ± 537 mg at 6 months).

DBS of the subthalamic nucleus (STN). The STN may be the preferred target site for stimulation or lesioning in PD[329] because it provides excitatory innervation to a variety of neuronal targets (SNc, GPi, PPN, SNr) in addition to the GPi,[352,353] and inhibition of STN overactivity has the potential to block excitatory damage to its target structures and to provide protective effects.[93] Therefore, it may be that stimulation of the STN might have more far-reaching consequences and provide superior clinical results compared to stimulation of the GPi or other targets.

In a preliminary clinical trial, bilateral DBS–STN was shown to be able to provide advanced PD patients with a full range of antiparkinsonian benefits.[371] Subsequent clinical trials showed that STN stimulation in the practically defined "off" state provided significant improvement in UPDRS, ADL, and motor scores (approximately 40 to 60%).[372,373] Benefits were seen with respect to tremor, bradykinesia, rigidity, and gait and were confirmed in a double-blind crossover evaluation in one study.[373] Stimulation improved UPDRS motor scores in the medication "on" state but benefits were less impressive than in the "off" state. Dyskinesia was markedly reduced (by approximately 80%) despite targeting the STN which, in theory, could have caused hemiballismus. This benefit may have related to the corresponding reduction in levodopa dose (25–50%) that accompanied STN stimulation.

The 6-month multicenter crossover study mentioned above evaluated 91 patients who underwent bilateral DBS–STN.[370] The study included a double-blind crossover evaluation at 3 months. In comparison to baseline, stimulation in the "off-medication" state was associated with an improvement of 47% in the UPDRS motor score ($p<0.001$). This benefit was confirmed in the double-blind crossover evaluations ($p<0.001$). Significant benefits were observed with respect to activities of daily living, tremor, rigidity, bradykinesia, and gait. Benefits also were observed with stimulation in the "on-medication" state but were of smaller magnitude. Home diary assessments revealed that the percentage of the waking day in "on" time without dyskinesia increased from 27 to 74% between baseline and 6 months ($p<0.001$) and the percentage of the day in "off" time decreased from 49 to 19% ($p<0.001$). Mean dyskinesia score

was also significantly improved ($p<0.001$), possibly as a result of a reduction in levodopa dose equivalents from a mean of 1,219 ± 575 mg at baseline to 764 ± 507 at 6 months. Physician and patient global assessments of severe disability fell from 74 and 77% at baseline to 15 and 23% at 6 months.

It is noteworthy that dyskinesia was significantly reduced by DBS of either the STN or the GPi, although the mechanism responsible for benefit may be different. DBS–STN permits a reduction in levodopa dosage that may account for its antidyskinetic effect. However, this would not account for the antidyskinetic benefit observed with stimulation of the GPi. It has been proposed that attenuation of dyskinesia with both of these procedures, and with pallidotomy, may be due to stimulation-induced obliteration of an abnormal neuronal firing pattern that is conveying misinformation from the basal ganglia to the cortical motor regions.[170]

Adverse effects associated with DBS. Adverse events associated with DBS can be divided into those related to the procedure, to the device, and to stimulation. Intracerebral hemorrhage with persistent neurologic deficit is the most serious adverse event, occurring in approximately 1–2% of patients undergoing DBS-Vim nucleus and in seven of 143 patients undergoing bilateral stimulation of GPi or STN (5% of patients and 2.5% of procedures). Device-related mechanical and infectious complications are relatively uncommon (approximately 2% of cases) but occasionally necessitate additional surgery to correct the problem or replace the lead. The majority of patients experience transient muscle twitch or paresthesia in the contralateral hand or face lasting for several seconds after the device is turned on. Other stimulation-related side effects are less common and include headache, disequilibrium, mild paresis, gait disturbances, and dysarthria. In almost all instances, these are attenuated with chronic stimulation or eliminated by stimulator adjustment. Only a few patients have to make a choice between better control of motor dysfunction and fewer stimulation-related side effects. Stimulation of STN and GPi induced transient dyskinesia in a few patients, but neither persistent dyskinesia nor hemiballismus occurred in patients in either group. Neuropsychological testing showed no deterioration after DBS–GPi procedures,[374] and STN stimulation did not induce worsening of cognitive function.[375] There is one report of stimulation-induced severe depression associated with STN stimulation.[376] Overall, DBS procedures are relatively well tolerated, with adverse effects similar to those observed with other stereotactic procedures for PD and fewer serious side effects than would be expected with bilateral ablative procedures.[314,330,337,377] The tolerability of bilateral DBS versus bilateral ablative procedures is one of its major advantages.

To minimize adversity and maximize benefit associated with DBS, it is important to be sure that the electrode is placed in the desired location. In the same patient, stimulation of the dorsal pallidum has been shown to worsen parkinsonian motor features whereas stimulation of the ventral GPi improved PD features.[378] Other studies have similarly shown that pallidal stimulation with improperly placed electrodes can worsen parkinsonian features[379] and that stimulation with electrodes presumably in the STN can lead to immediate and severe depression.[376] These findings argue for further studies to better map the sensorimotor regions of the GPi and STN and for the use of microelectrode recordings to ensure that the desired target site has been chosen. See therapeutic breakout 9 for the advantages and disadvantages of DBS procedures.

Fetal transplantation. Fetal transplantation as a treatment for PD is based on the notion that embryonic dopaminergic neurons implanted into the denervated striatum can survive and compensate for degenerating SNc neurons. Laboratory studies have demonstrated that implanted fetal nigral neurons can survive, produce dopamine, extend axons, and provide behavioral benefits in the 6-OHDA rodent and MPTP-treated monkey (see reviews in Lindvall[318] and Olanow et al.[319]). These studies have served as the basis for initiating clinical trials in PD patients. There are many transplant variables that can influence whether or not implanted cells survive and clinical benefits ensue. These include the number of donors, the donor age, method of storage of tissue, site of implantation, distribution of tissue, and use of immunosuppressants. Clinical trials to date have used a variety of different transplantation regimens and, not surprisingly, have produced variable clinical results. However, using protocols designed to maximize survival of implanted cells, long-term meaningful clinical benefit and an increase in striatal FD uptake on PET have been observed in open-label studies by several groups.[380-382] Benefits observed include improvement over baseline in motor function during "off" stages and increased "on" time without dyskinesia. These benefits have been shown to persist over years and to be associated with a progressive increase in striatal FD uptake.[380,383]

Postmortem studies support the potential of fetal nigral transplantation to benefit PD patients. Autopsy studies in PD patients who had experienced substantial clinical benefit after fetal nigral transplantation procedures showed robust survival of implanted neurons, with extensive dopaminergic innervation of the target region in an organotypic fashion.[384,385] In transplanted regions, there was normal staining for tyrosine hydroxylase (TH) and dopamine transporter, normal TH mRNA expression, and normal-appearing synaptic connections between host and graft (figure 19).[129,385] These findings demonstrate the potential of transplanted fetal nigral cells to reinnervate a target region that has been denervated by the neurodegenerative process in PD.

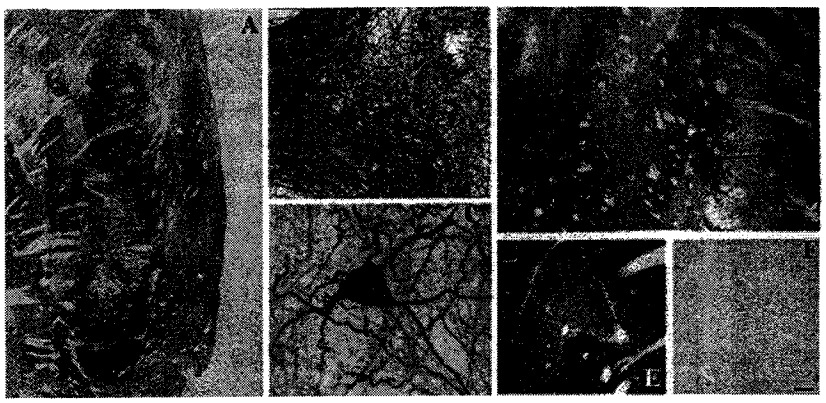


Figure 19. Transplant postmortem. (A) Low-power THir-stained graft deposit. Each graft deposit had a similar appearance. (B) Higher-power view demonstrating THir-stained dopamine neurons with many fiber processes extending from the graft into the striatum. (C) High-power view of individual THir-stained grafted neuron demonstrating that it has the triangular appearance and neuronal extension characteristics of a dopaminergic neuron. There were 82,000–138,000 THir-positive cells per putamen. (D) Low-power view demonstrating THir innervation of the striatum with seamless integration between graft deposits and (E) a typical patch-matrix appearance. (F) Lack of THir-staining in nontransplanted region of the striatum. (Adapted with permission from Reference 384).

To better assess the safety and efficacy of fetal nigral transplantation in PD, two NIH-sponsored prospective, randomized, placebo-controlled, double-blind studies have been performed. The first involved 40 patients who were implanted bilaterally into the caudate and putamen with two donors per side, without using immunosuppression.[386] The primary end point was the change from baseline in quality of life, and it was not improved in transplanted patients in comparison to controls. There was significant improvement in UPDRS motor and ADL scores, particularly in patients under 60 years of age. Striatal FD-PET was significantly increased in transplanted patients but, again, primarily in younger patients.[387] The second is a 2-year placebo-controlled, double-blind study.[388] It compares the results in patients who receive bilateral transplantation into the postcommissural putamen with one or four donors per side to patients receiving a cosmetic placebo operation. In this study, tissue is more densely and evenly distributed throughout the target region and immunosuppression with cyclosporine is employed. The study is scheduled for completion in the fall of 2001.

Reports of published studies to date suggest that transplantation is well tolerated and that there are few serious adverse events. There is one report of death consequent to migration of the fetal tissue graft into the posterior fossa with obstruction of the fourth ventricle.[389] Histologic examination showed the presence of bone, hair, cartilage, and epithelium within the graft, indicating that the wrong tissue was dissected out and implanted. This case emphasizes the necessity of expertise in neurology, neurosurgery, and transplant biology before performance of these procedures.[390] Of greater concern is the report of disabling dyskinesia that persists throughout the medication "off" stage in patients who had undergone a transplantation procedure.[386,391] The frequency, clinical significance, and basis for this problem remain unknown but clearly warrants further investigation.

Aside from the need to determine the safety and efficacy of transplantation in PD, there are societal and logistic concerns regarding the use of human fetal tissue. Accordingly, there has been an extensive search for alternate sources of dopaminergic cells and rescue-oriented strategies. Xenografts, using embryonic porcine dopaminergic cells, have been tested in a few patients with limited success,[392] and a prospective, double-blind controlled study has been performed. Preliminary, unpublished reports indicate that the study was negative. Laboratories have also begun to focus on strategies designed to rescue or restore dopaminergic function using trophic factors, stem cells, and gene therapies.

Several hundred PD patients have now undergone transplant procedures, but they are only performed at a limited number of centers. The technique offers promise as another possible treatment option for PD patients who fail medical therapy. Indeed, the theoretical potential to improve PD features by restoring dopaminergic innervation to the striatum without making a destructive lesion or requiring an electronic stimulator makes transplant particularly appealing. For the present, however, transplant must be considered an experimental procedure, and it cannot be recommended for routine clinical use. The advantages

***Therapeutic Breakout 10** Transplantation*

Advantages
Consistent clinical benefit with some transplant protocols
Consistent increase in striatal FD uptake on PET scan
Implanted cells survive and reinnervate the striatum in an organotypic manner
Does not necessitate making a destructive lesion in the brain
Disadvantages
Necessitates needle passage(s) through the brain, with risk for hemorrhage
Optimal transplant variables not yet defined
Optimal target site not yet defined
Societal and logistic concerns regarding the use of fetal cells
Limited number of centers that can utilize this technology
Reports of disabling dyskinesia need to be clarified

Table 8 Relative merits of different surgical procedures for PD[392a]

Procedure	Tremor	Rigidity/bradykinesia	Dyskinesia	Adverse events*
Thalamotomy	+++	+/−	+/−	3
Pallidotomy	++	++	+++	3
DBS–thalamus	+++	+/−	+/−	2
DBS–GPi	++	+++	+++	2
DBS–STN	+++	+++	+++	2
Fetal nigral transplantation	++	++	++/−	1

+ = mild benefit; ++ = moderate benefit; +++ = marked benefit.

* For bilateral procedures, 1 = minimal risk; 2 = more pronounced risk; 3 = greatest risk.

and disadvantages of fetal nigral transplantation are summarized in therapeutic breakout 10.

Who is a candidate for surgery? What is the best surgical procedure? It has not yet been clearly established precisely who is the ideal candidate and when is the optimal time for performing a surgical intervention in PD. For patients with advanced disease who can no longer be adequately controlled by medical therapy, who have a poor quality of life, and who are cognitively intact, surgery is a definite consideration.[392a] In this situation, it is becoming increasingly clear that the risk:benefit ratio is in the patient's favor. Surgery also may be helpful for patients with less severe disease but who are experiencing motor complications and functional disability that cannot be adequately controlled with antiparkinsonian medication. Here, however, one must be cognizant of the risk for inducing complications in a relatively intact individual and the potential of an intracranial surgical procedure to make a functioning patient worse.

Relative contraindications to surgery include patients with advanced age, co-morbidities, cognitive impairment, and speech dysfunction, because these all increase risks. There is no evidence that any of the surgical procedures provide benefits that are any better than the best that can be obtained with levodopa, but they do have the potential to alleviate the motor complications that prevent patients from experiencing the full benefit of the medication. With respect to the optimal candidate for a surgical procedure, these would appear to be patients who continue to experience a good response to levodopa but cannot be satisfactorily controlled because of motor fluctuations and dyskinesia. Those parkinsonian features that respond to levodopa, such as tremor, bradykinesia, and rigidity, are the ones that benefit most from surgical procedures. It is less clear if surgery also benefits features such as gait dysfunction, freezing, and postural instability, which do not respond well to levodopa.

As the long-term safety and efficacy profiles of the different surgical procedures become more clearly defined, it may be easier to resolve some of these issues, and it is possible that surgery will be employed earlier in the course of the disease. If surgical intervention can be shown to restore functions that levodopa cannot treat or to provide neuroprotective benefits, this would further support its earlier use.

In trying to compare the different surgical treatments for PD, it is important to appreciate that most current information derives from unblinded, nonrandomized, anecdotal studies involving small numbers of patients. There have been few double-blind, randomized, prospective, or controlled trials of any of these procedures and literally no well-designed studies aimed at directly comparing them. Part of the problem has been the reluctance of the surgical community to perform placebo-controlled surgical trials for "ethical" reasons.[388] This situation is changing. The NIH has funded two prospective, randomized, double-blind, placebo-controlled trials of human fetal nigral transplantation in PD. The FDA has mandated the use of a double-blind, placebo-controlled protocol for the trial of fetal porcine nigral transplantation. A double-blind, controlled study design was used to demonstrate that DBS–Vim nucleus and thalamotomy provide comparable antitremor effects but that the DBS procedure provided greater functional benefits. A prospective multicenter, randomized, double-blind crossover study of DBS of the STN and GPi showed significant benefit with stimulation of either target. Because patients were not randomized to treatment groups, the study was not designed to directly compare the two procedures. Similarly, DBS–STN and DBS–GPi have not been formally compared to other surgical procedures.

These constitute the studies that are available to aid the physician in selecting an operative procedure for a PD patient who cannot be satisfactorily controlled with medical therapy. With such scant data to rely on, determination of a surgical procedure for an individual patient is often a matter of judgment. Surgery usually is recommended because of disability related to the motor complications associated with chronic levodopa therapy. This reinforces the importance of utilizing strategies in the early stages of the disease that reduce the risk for development of motor complications. Our view of the relative merits of the different surgical approaches is provided in table 8.

Principles that we have applied in trying to deter-

mine who is a candidate for surgery and which surgical procedure to perform on an individual patient are as follows:[392a]

1. Ensure correct diagnosis. Many parkinsonian patients referred for surgery are doing poorly because they have atypical parkinsonism. There is no evidence that any of the surgical procedures are of value for patients with atypical parkinsonism.
2. Ensure preserved cognitive function preoperatively so that patients can give informed consent and to minimize the risk for inducing further cognitive impairment.
3. Stimulation procedures are generally preferred to lesions, especially if bilateral surgery is required.
4. DBS–STN and DBS–GPi provide comparable benefits even for patients with dyskinesia.
5. DBS–STN is preferred to DBS–Vim nucleus. Both procedures provide excellent antitremor effects, but DBS–STN offers the advantage of controlling other parkinsonian features if they are already present or should they develop at a later time. As a result, DBS–Vim nucleus is rarely performed for PD at present.
6. Transplantation may restore motor function in a more physiologic way than can be accomplished with other surgical procedures, but it still must be considered an experimental procedure.

OTHER ISSUES IN THE MANAGEMENT OF PD

Neuropsychiatric problems. Mental symptoms such as dementia, delirium, and depression may occur at one time or another in the majority of PD patients and can potentially be more disabling than motor dysfunction. Dementia and delirium are the leading causes of nursing home placement among PD patients.[393] Some of these neuropsychiatric problems, such as hallucinations, memory loss, confusion, and dementia, may be part of the disease process itself but may also be aggravated by antiparkinsonian and other medications and by concurrent illness. Anxiety and depression might be an inherent part of the disease process, but might also occur in response to having a chronic, progressive, neurodegenerative illness; in this context, they might be improved by antiparkinsonian, antidepressant, and sedative medication. Therefore, in devising a rational approach to the treatment of the neuropsychiatric problems that occur in PD, a decision must be made about whether to add to or reduce psychoactive medications and whether to add to or reduce the dosage of antiparkinsonian agents.

Cognitive impairment and dementia. Cognitive impairment is commonly associated with PD. In its severe form, it may be global and may meet *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV) criteria of dementia. Alternatively, it may be milder and represent a more selective deterioration in cognitive abilities. It has been proposed that PD patients have a subcortical dementia with preferential involvement of construction, visuospatial performance, memory, thought processing, and verbal fluency, and a relative sparing of language and social behavior. Formal neuropsychiatric evaluations may be required to recognize and define the problem in an individual patient. The Mini-Mental Status Examination (MMSE) is a simple means of assessing cognitive impairment that provides a rapid measure of spatial and temporal orientation, attention span, language function, and constructional praxis.[394] An MMSE score of 24 or less is suggestive, but not diagnostic, of dementia. In contrast, an intact MMSE score does not exclude a selective impairment in cognition. Specific tests of language function, visuospatial relations, speed of information processing, and executive function (i.e., planning, sequencing, innovating) may be needed to detect selective cognitive impairment. This may not be apparent to the patient, and questioning the family or formal neuropsychologic testing may be necessary to identify the problem.

Overt dementia develops in approximately 30% of PD patients, depending on age, disease duration, and the population surveyed,[395-399] and this number probably underestimates the true frequency.[400] A community-based population study estimated that dementia affected 41.3% of the PD population.[401] A prominent age effect was observed, with the prevalence of dementia increasing from 12.4% in the 50- to 59-year age group to 68.7% in those over 80 years of age. A prospective, longitudinal, clinical study showed that PD patients were more likely to develop dementia than controls.[402] Nineteen percent of PD patients followed for 37 months, but no age-matched control patients, developed a newly diagnosed dementia that met *Diagnostic and Statistical Manual, 3rd edition revised* (DSM-III-R) criteria. The magnitude of this number is all the more appreciated when one considers that patients with cognitive impairment were specifically excluded from the study and that patients were followed for only a relatively short time. The prevalence of dementia in PD patients can therefore be estimated to be approximately 6- to 12-fold greater than in age-matched controls. PD patients who develop dementia tend to be older, to develop PD at an older age, to have a longer duration of disease, and to have a greater likelihood of having antecedent hallucinations than nondemented PD patients.[402-404] More subtle cognitive impairment without obvious dementia occurs in at least an additional 20% of PD patients.[405-407] Manifestations can include impairment or slowness of information processing (bradyphrenia), altered executive functions, memory loss, decreased attention span, and inappropriate behavior, with or without delirium.

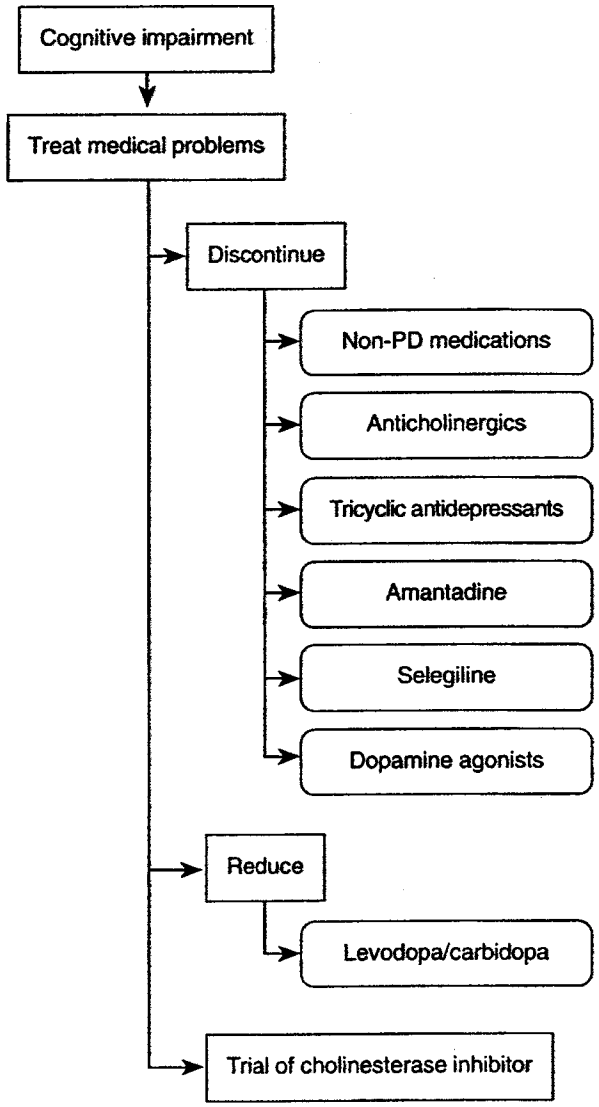
Cognitive impairment in PD patients may arise from damage to dopaminergic neurons in the SNc (especially the medial nigra), noradrenergic neurons in the locus ceruleus, cholinergic neurons in the nucleus basalis of Meynert, or cortical degeneration. Neurodegeneration accompanied by Lewy bodies oc-

curs in each of these structures in PD. In addition, Alzheimer's disease (AD) pathology is more frequently encountered in PD patients than in controls. In one study, 55% of PD patients with autopsy confirmation had mild to moderate dementia during life.[408] In these patients, 42% also had senile plaques and neurofibrillary tangles consistent with a diagnosis of AD. This is six times the expected prevalence for an aged-matched control population. In a second study, senile plaques were found in 29/34 (85%) PD patients but in only 5/34 (15%) control subjects.[409] Along these lines, patients diagnosed as having AD are more likely than controls to develop parkinsonian motor features during life and to have PD pathology at postmortem.[410,411] This overlap between PD and AD has caused some to speculate on the possibility that these two neurodegenerative conditions share common etiologic and/or pathogenetic mechanisms.[412] Parkinsonism and dementia also have been described in conjunction with pathologic evidence of diffuse cortical Lewy bodies.[413-415] It remains to be determined if this condition represents a new disease entity or is simply part of a spectrum of neurodegeneration that includes PD and dementia.[412]

Dementia is not commonly described during the first 1 to 5 years after the diagnosis of PD. This may simply represent a tendency to diagnose PD only if motor features come first and to diagnose patients as having diffuse Lewy body disease (DLBD) or AD if dementing features antedate the development of PD features or appear early in the course of the illness. Indeed, although dementia is reported to be rare in the early stages of PD, minor cognitive impairment and/or hallucinations are commonly seen in early PD patients[405-407] and are risk factors for subsequent development of dementia.[404]

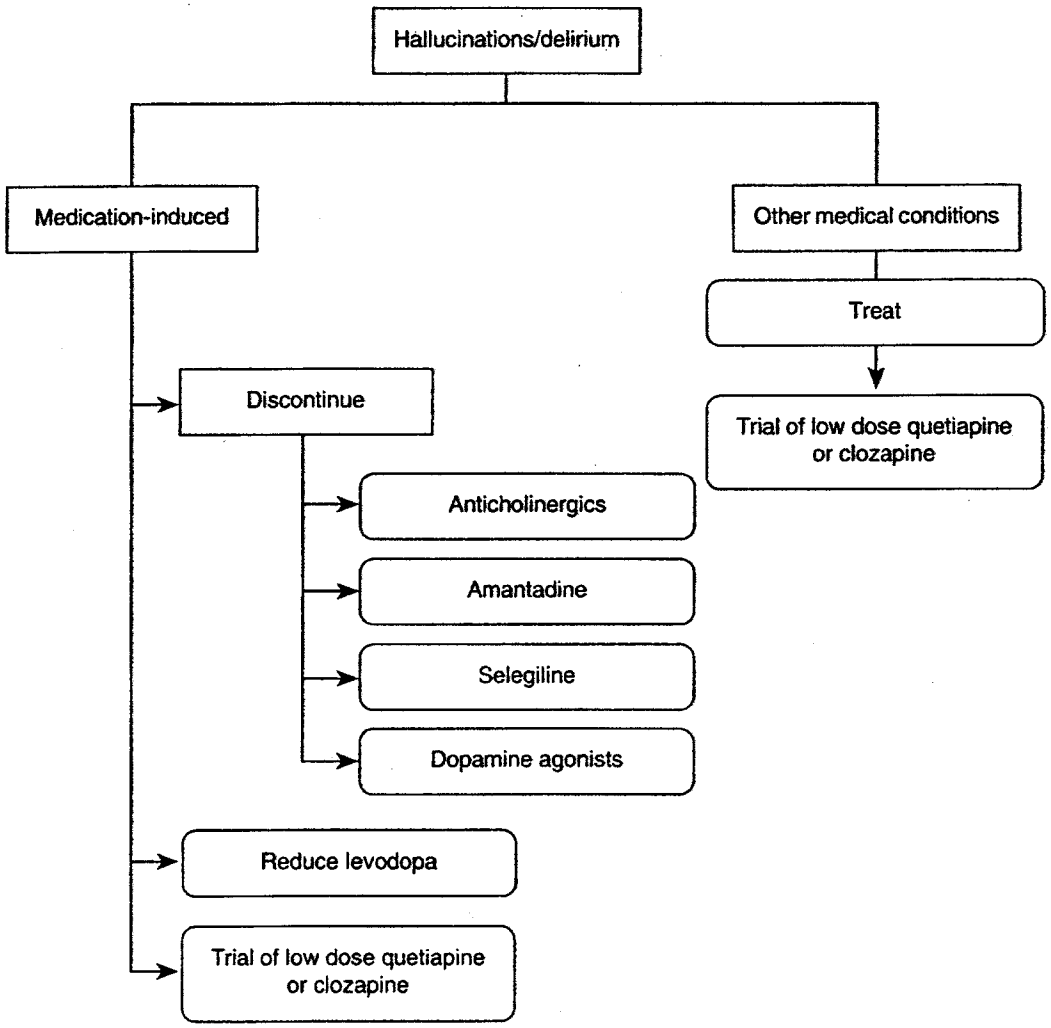
Patients with cognitive impairment do not tolerate metabolic disorders, dehydration, sedative and anxiolytic medications, and antiparkinsonian drugs.[416,417] Anticholinergic agents and amantadine are particularly prone to worsen confusion and promote psychotic features in cognitively impaired patients. Depression also is common in PD[418] and may complicate accurate diagnosis of cognitive impairment.[419,420] PD patients may suffer from a syndrome of apathy, decreased energy, and passivity that simulates depression but does not respond to antidepressants and is not associated with guilt, helplessness, remorse, or sadness.

Management of the cognitive impairment associated with dementia involves the following steps to be taken in sequential order (breakout 9):



Breakout 9. Cognitive impairment can take the form of a selective impairment in memory or frank dementia. Management consists of treating any underlying medical problem and reducing or eliminating any offending medication. Nonessential, nonantiparkinsonian drugs should be discontinued first, particularly sedatives or anxiolytics. The antiparkinsonian drug with the most potent anticholinergic properties should then be eliminated, followed by amantadine, selegiline, and dopamine agonists. If cognitive impairment persists, the levodopa/carbidopa dosage should be reduced. Ultimately, a balance must be reached between the adverse effect of the drug on mental function and its beneficial effect on PD. In some patients, no medication adjustment can ameliorate the dementia or the delirium associated with cognitive impairment. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

- Correct underlying problems, such as infection, dehydration, electrolyte imbalance, or other metabolic abnormalities.
- Review drug history and eliminate unnecessary medications. In particular, sedative and anxiolytic medications should be withdrawn if possible.
- Gradually decrease or discontinue antiparkinsonian medications in the following order depending on response: anticholinergic agents, amantadine, selegiline, and dopamine agonists.
- If, despite the above, the patient continues to experience confusion and/or hallucinations, gradually



Breakout 10. Hallucinations in PD patients can occur spontaneously or can be induced by medication in a cognitively impaired patient. The management of drug-induced hallucinations is a sequential series of steps that includes:

Discontinuation of unnecessary nonparkinsonian medications

Discontinuation of antiparkinsonian agents in the following order: anticholinergics, amantadine, selegiline, and dopamine agonists

Reduction of the dose of levodopa to balance improvement in delirium or psychosis with the reemergence of parkinsonism

If hallucinations persist, consider a trial of low-dose quetiapine or clozapine, atypical antipsychotics with a low potential for exacerbating parkinsonian symptoms. During clozapine treatment, patients must be monitored for side effects, such as orthostatic hypotension and agranulocytosis, and they require weekly blood tests. Clozapine or quetiapine will not improve dementia.

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lower the dose of levodopa. Ultimately, a judgment may have to be made in choosing between cognitive benefits obtained by reducing the dose of levodopa and any worsening of parkinsonian features.

Consider a trial of a cholinesterase inhibitor such as donepezil (Aricept) or rivastigmine (Exelon). Preliminary open-label studies suggest they might have the same level of benefit they offer in AD (i.e., slight) in PD, especially in early patients.[421] There is, however, some suggestion that they also may worsen parkinsonian features.

Ensure that adequate home care can be provided and that the needs of the caregiver are considered.

If demented patients cannot be satisfactorily controlled with these actions, nursing home placement may have to be considered.

The management of patients with selective cognitive impairment is similar to that for dementia (see breakout 9). Proper treatment of these patients is particularly important because they may still be able to function independently if managed correctly. Particular attention should be paid to avoiding drugs

that can adversely affect mental function and treatment of intercurrent medical problems. Anticholinergic drugs, amantadine, and sedative medications can induce or worsen selective cognitive impairment and should be gradually withdrawn if possible. Parkinsonian features in patients with cognitive impairment should be treated with regular formulations of levodopa at the lowest dose that provides an acceptable level of motor benefit and, ideally, that does not worsen cognitive performance.

Hallucinations and delirium. Hallucinations occur in 20% of PD patients, and the incidence increases with age and with the degree of cognitive impairment.[422] They may develop in any stage of PD, and may occur spontaneously or, more commonly, secondary to antiparkinsonian, anxiolytic, sedative, antidepressant, or other neuropsychiatric drugs. They are usually more pronounced at night and are typically visual, although rarely they can be somesthetic or auditory. They tend to consist of formed images, such as a friend, a family member, or a pet, that are not threatening to the patient but that are usually more upsetting to the family. In more advanced states, hallucinations can be frightening. Patients who experience hallucinations are prone to go on and develop a frank dementia. The presence of hallucinations may also limit the ability of the physician to increase dopaminergic therapy to more satisfactorily control parkinsonian motor dysfunction.

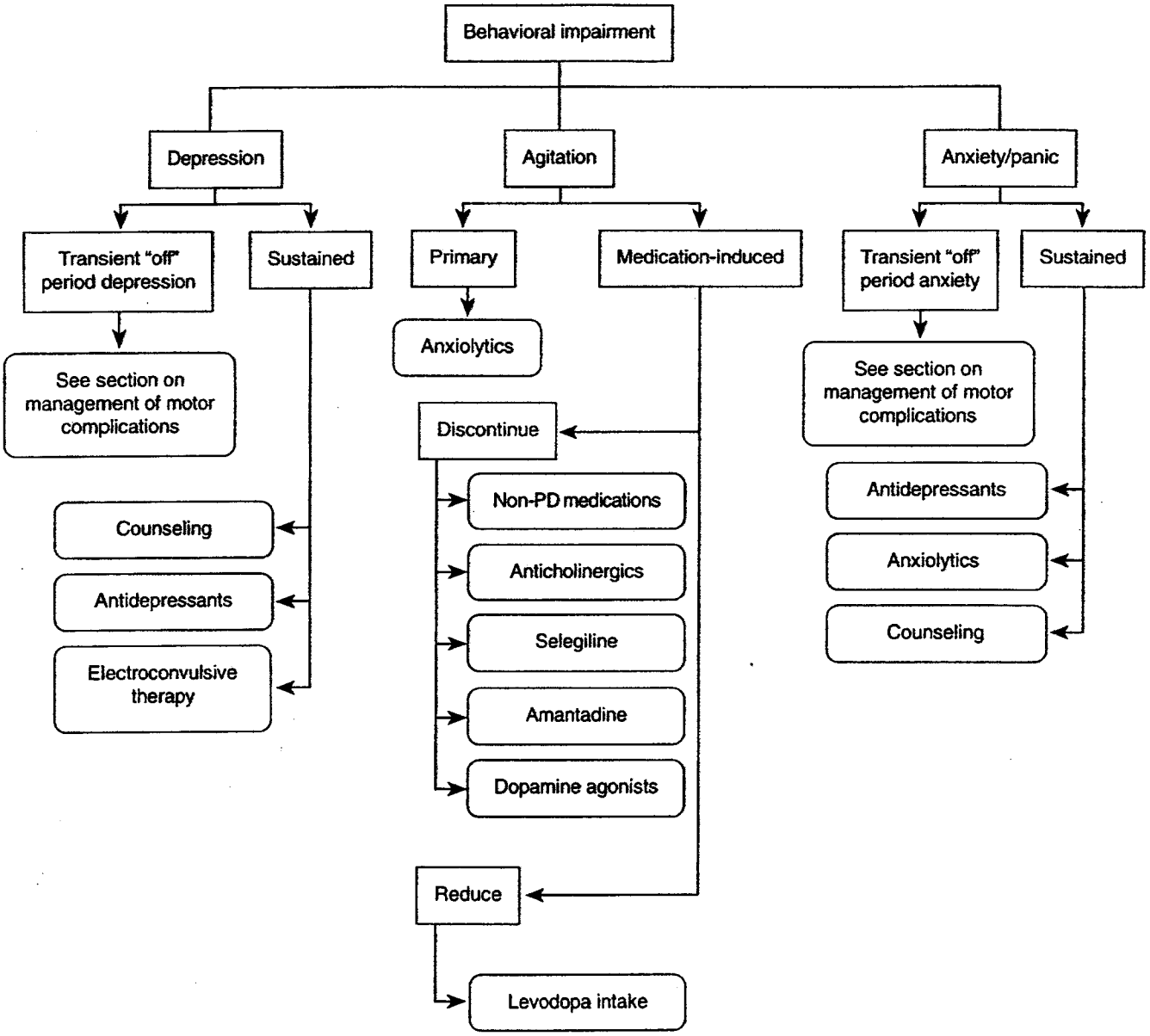
In some patients, the onset of delirium is insidious or does not progress beyond a mild stage. In others, delirium may develop acutely over hours and worsen rapidly, particularly when there is an underlying medical problem or a rapid change in medication.[423] At first, patients may be restless and distractible, beginning a second task before they have completed the first. Behavior may be obsessional, fearful, or inappropriate. They may have vivid dreams or nightmares and may experience disruption of sleep with a reversal of the sleep cycle, such that they sleep during the day and stay awake during the night. In more advanced cases, patients can experience agitation, delusions, paranoid ideations, and frank psychosis.

The management of delirium in the PD patient (breakout 10) is similar to the management of cognitive dysfunction and should be approached in a stepwise fashion utilizing the following steps:

1. Eliminate other causes of delirium, including infection, dehydration, electrolyte imbalance, or a structural lesion of the brain (e.g., subdural hematoma).
2. Discontinue nonparkinsonian psychotropic medications whenever possible. Many drugs frequently employed in PD patients have anticholinergic properties and can induce psychosis. These include tricyclic antidepressants, bladder antispasmodics [e.g., oxybutynin (Ditropan)], and muscle relaxants [e.g., orphenadrine (Norflex)].
3. Eliminate antiparkinsonian drugs with the most delirium-inducing potential and the least antiparkinsonian activity in the following order: anticholinergics, amantadine, selegiline, dopamine agonists, and levodopa/carbidopa. The anticholinergic drugs are the most likely to induce delirium and should be withdrawn first. Antiparkinsonian medications should be reduced to the point of improving delirium without drastically worsening parkinsonism if possible. Reduction or discontinuation of bedtime medication may alleviate nighttime hallucinations. It is best to reduce antiparkinsonian medications gradually because sudden withdrawal of dopaminergic agents can lead to a neuroleptic malignant syndrome.[424]
4. Use the regular formulation of levodopa at the lowest dose that provides satisfactory control of parkinsonian motor features. The levodopa dose should be reduced only if hallucinations persist after elimination of all other antiparkinsonism agents. In some patients it may be necessary to choose between lowering the dose of levodopa to improve mental function and maintaining the dose to manage motor dysfunction, while accepting neuropsychiatric complications.

When the above adjustments fail to eliminate or sufficiently alleviate hallucinations and/or cannot be accomplished without inducing a meaningful deterioration in PD features, neuroleptic therapy should be considered. Haloperidol (Haldol), perphenazine (Trilafon), and chlorpromazine (Thorazine) are effective antipsychotics but are not recommended for PD patients because of their capacity to block striatal dopamine D_2 receptors and exacerbate parkinsonian features. A group of more selective or "atypical" neuroleptics has become available that greatly improves the ability to treat hallucinations and psychosis induced by dopaminergic medications.[425] They have been called "atypical" because they block limbic and cortical D_3, D_4, and D_5 receptors, but they are relatively devoid of D_2 receptor-blocking properties. Therefore, in principle, they can ameliorate or eliminate dopamine medication-induced psychotic features without worsening parkinsonism. The best studied of these agents is clozapine (Clozaril).[425-428] Both open-label and double-blind, placebo-controlled trials have demonstrated that clozapine can reduce hallucinations in PD patients without worsening parkinsonian motor features. Control of psychosis may also enable higher doses of levodopa to be employed, with a resulting improvement in motor function. Anecdotal reports of antidyskinesia effects with clozapine have not been confirmed.[429]

All neuroleptic drugs are sedating, and a key to success when they are used in PD patients is the use of low doses.[428] It is recommended to start clozapine with a very low dose at bedtime and then gradually to escalate the dose every 3–5 days until hallucinosis/psychosis are controlled and the normal sleep–wake cycle has been restored. The dose of clozapine required to treat dopamine-induced hallucinations is



Breakout 11. Behavioral impairment can take the form of depression, agitation, anxiety, or panic attacks. For depression; *life-style concerns should be addressed. Pharmacotherapy can include the SSRIs or TCAs. The latter have anticholinergic properties that may impair mental function. It has been recommended to avoid combining an SSRI with selegiline because of the risk of inducing a serotonin syndrome or a "cheese reaction," but this has not been established. Electroconvulsive therapy may be effective as a last resort for patients with refractory depression.* Agitation *can be treated with low doses of a short-acting anxiolytic. Drug-induced agitation is managed by discontinuing any causative nonparkinsonian drugs and then discontinuing antiparkinsonian agents in the order of their potential to cause agitation. For* anxiety and panic attacks, *if they occur during "off" periods, antiparkinsonian medications should be used to try and decrease "off" time. If this fails or if anxiety or panic persists, a trial of an anxiolytic drug, such as a short-acting benzodiazepine or buspirone, is warranted. Cognitively impaired patients may not tolerate these drugs. If the benzodiazepines are ineffective, then a TCA or an SSRI may be used, especially if the anxiety is part of an agitated depression. Adapted with permission from* Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

much lower than that used to treat schizophrenia, which ranges from 200 to 600 mg/day. In PD, clozapine therapy is started with a dose of 6.25 to 12.5 mg at bedtime (a quarter to half of the 25-mg tablet) and gradually increased to 25 to 75 mg per day depending on response. It is rare to need more than 100 mg of clozapine to control hallucinations or psychosis in PD patients,[425,426] but higher doses may be required if hallucinations are unrelated to antiparkinsonian medications or are related to a preexistent psychotic disorder. Control of hallucinations may further benefit PD patients by enabling them to tolerate higher doses of levodopa and thus to obtain further improvement in parkinsonian status. It is important to appreciate that neuroleptics such as clozapine are not effective for treatment of confusion or dementia.

Patients with moderate to severe dementia may demonstrate a paradoxical worsening of psychosis and confusion. Cognitively impaired patients also may become drowsy on clozapine. If this occurs, the majority of the daily dose can be given at night. Clozapine can also cause orthostatic hypotension, and the first dose should be given with the patient in a supine position, preferably at night when the patient is in bed. At higher doses, patients may experience seizures and severe sialorrhea. *The most serious complication of clozapine is agranulocytosis, which occurs in approximately 1–2% of patients and is not dose-related. For this reason, in the United States, regulatory agencies have mandated that clozapine-treated patients must have weekly white blood cell counts for the first 6 months of therapy and biweekly thereafter.*

Newer selective antipsychotic agents that do not induce hematologic side effects are being evaluated in PD patients as alternatives to clozapine. Quetiapine (Seroquel) appears to be the most promising of these. In one study, 20/24 patients initiated on neuroleptic therapy with quetiapine in a dose of approximately 45 mg per day experienced marked improvement in psychosis without worsening of parkinsonism.[430] Quetiapine should be initiated at a dose of 12.5 mg (half of a 25-mg pill) at bedtime and titrated at 3- to 5-day intervals until the desired effect is achieved or side effects emerge. Similar results were observed in 15 patients treated with olanzapine (Zyprexa),[431] a selective neuroleptic with dopamine- and serotonin-blocking properties. Olanzapine should be prescribed at low doses in PD patients and administered as a single dose at bedtime. Until recently, tablet sizes were too large (5 and 10 mg) for effective use in PD, for which smaller doses are required. Tablets of 2.5 mg are now available, and a quarter to a half of this tablet can be used to initiate therapy at bedtime. Olanzapine in high doses has D_2 receptor-blocking properties and has been shown to induce worsening of parkinsonism. In addition, olanzapine provided inferior antipsychotic results in comparison to clozapine in a double-blind trial.[432] As with other neuroleptics, somnolence is a major side effect, with mean sleep time being increased by 45% over baseline. Risperidone (Risperdal) has been shown to worsen parkinsonian motor features and was also less effective than clozapine in a comparative study.[433] Ondansetron (Zofran) and granisetron (Kytril) are serotonin 5-HT_3 receptor antagonists that have been used primarily to treat the vomiting associated with cancer chemotherapy. A preliminary open-label trial reported that ondansetron could provide antipsychotic benefits to hallucinating PD patients.[434] Ondansetron is well tolerated and does not cause drowsiness or orthostatic hypotension. In addition, it can be given parenterally and therefore may be useful in the management of postoperative delirium in PD patients. However, this agent is extremely costly, and additional clinical experience is needed before it can be recommended in PD.

On balance, clozapine still appears to be the most effective agent for treating drug-induced psychosis in PD patients, but the need for monitoring and the risk for hematologic side effects detract from its utility. Of the new antipsychotic agents that do not require laboratory monitoring, quetiapine appears to be the most promising. Double-blind controlled trials to confirm the utility of quetiapine for treating psychosis in PD are required.

Behavioral impairment and mood disturbance. Behavioral impairment/mood disturbance in PD can take the form of depression, anxiety, panic attacks, or agitation (breakout 11). In some patients, mood changes occur in synchrony with motor fluctuations, causing the patient to feel depressed or agitated during the "off" state. In this case, management consists of strategies designed to reduce motor fluctuations (see section on Management of Motor Complications). In parkinsonian patients with major depression, management consists of counseling, antidepressants and, in the more severe and treatment-resistant cases, electroconvulsive therapy (ECT), which also may provide short-term antiparkinsonian effects.

If patients experience anxiety, agitation, or panic attacks only during "off" periods, better control of parkinsonism may ameliorate these problems (see section on Management of Motor Complications). Unnecessary medications should be reduced or eliminated because of their potential to cause agitation. If patients suffer persistent anxiety, agitation, or panic attacks, low doses of a short-acting anxiolytic medication may be helpful.

Depression. Depression is pervasive in PD, and approximately 40% of patients suffer from depression at least once during the course of their disease.[418-420,435-438] As in other conditions, depression in PD is characterized by feelings of guilt, helplessness, remorse, and sadness. The depression in PD is independent of age, disease duration, disease severity, or cognitive impairment. Depression may be underdiagnosed or overdiagnosed in PD. The physical appearance of a PD patient can mimic that of depression. Therefore, a PD patient with hypomimia, hypophonia, psychomotor retardation, and a stooped posture may appear to be depressed but actually is not. Similarly, depression may be underdiagnosed because symptoms such as loss of energy, loss of appetite, loss of libido, and insomnia may be mistakenly attributed to PD. A structured interview with the patient and spouse, the use of a depression rating scale, and a psychiatric consultation may be helpful in arriving at a correct diagnosis. Depression may also be mistaken for dementia, may occur concurrently with dementia, or may be a forerunner of a developing dementia.[435,436,438]

It is uncertain whether depression in PD is endogenous, exogenous, or both.[420] Endogenous depression might occur as a result of the monoamine deficiency that characterizes PD, and exogenous depression is liable to occur in a patient who suffers from a chronic, progressive neurodegenerative disease. PD

patients are also in an age group in which depression is prone to occur for other reasons, such as retirement or loss of a loved one. These concerns, when present, must be addressed.

Both exogenous and endogenous forms of depression can therefore be linked to PD symptomatology and may be improved by antiparkinsonian treatment both in newly diagnosed patients and in patients with motor fluctuations who suffer depression during "off" periods. Treatment of PD should be the first step before considering more specific antidepressant therapy unless the patient suffers from profound depression. PD patients who experience sustained depression despite adequate antiparkinsonian therapy may require psychotherapy, antidepressants and, in more extreme circumstances, ECT. The tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline (Zoloft), paroxetine (Paxil), and fluvoxamine (Luvox) are the major treatment options. On the one hand, SSRIs are effective antidepressants that avoid the anticholinergic side effects associated with the TCAs and are generally preferred in the treatment of the PD patient. On the other hand, the SSRIs in general, and fluoxetine in particular, can be activating. This may be desirable in patients who are apathetic or withdrawn but undesirable in agitated patients. In addition, fluoxetine has an extended elimination half-life and an active metabolite that may cause side effects to persist even after drug withdrawal. The doses of SSRIs used to treat depression in PD patients are the same as for other causes of depression in the general population: fluoxetine or paroxetine (20–40 mg per day) and sertraline (50–150 mg per day) is usually sufficient. There have been isolated case reports of extrapyramidal symptoms (akathisia, dystonia, parkinsonism, and tardive dyskinesia) and worsening of parkinsonism with the SSRIs.[439,440] These have mostly been reported with fluoxetine but are rare occurrences and generally do not restrict the use of these drugs in PD patients. Jitteriness and increased tremor also may be seen with SSRIs in some PD patients. Concern has been raised about administering SSRIs in conjunction with selegiline for fear of inducing a serotonin syndrome or a hypertensive crisis,[441] but if this occurs it must be extremely rare. In a survey of Parkinson Study Group investigators, a serotonin-like syndrome was noted in only 11 of 4,568 patients (0.24%) receiving both selegiline and an SSRI, and in only two (0.04%) of these patients was the syndrome considered to be serious.

The TCAs and tetracyclic antidepressants also are effective in the management of depression. However, they are associated with anticholinergic effects and orthostatic hypotension, both of which may limit their usefulness in PD patients. They also have sedative properties that can be detrimental to apathetic patients but advantageous for those with anxiety or insomnia. Clinically, the propensity to induce sedation among TCAs can be ranked as follows: mirtazapine (Remeron; most sedative), doxepin (Sinequan), imipramine (Tofranil), desipramine (Norpramin), trazodone (Desyrel), and nortriptyline (Pamelor, Aventyl; least sedative). Nortriptyline, desipramine, and trazodone have less anticholinergic activity than the others and are cleared more rapidly. For these reasons they are the preferred agents in this class of drug. For purposes of facilitating sleep, nighttime doses of nortriptyline 20–40 mg, desipramine 25–50 mg, and mirtazapine 7.5–30 mg can be useful.

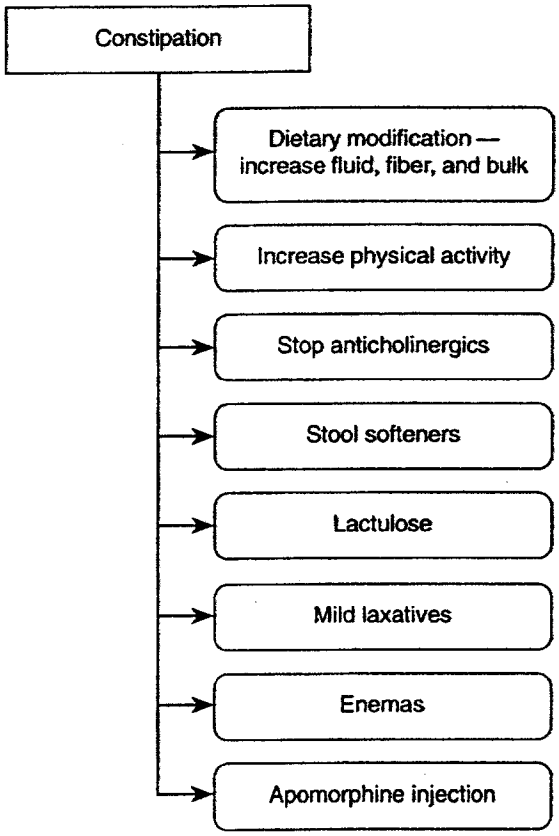
There is also recent information indicating that the dopamine agonist pramipexole is an effective antidepressant agent in both PD and non-PD patients. In a prospective double-blind trial performed in patients with major depression, pramipexole at doses of 1 and 5 mg per day yielded benefits comparable to those obtained with fluoxetine.[226] Statistically significant improvement was observed with pramipexole for all outcome measures used (Hamilton Depression Scale, Montgomery Asberg Depression Rating Scale, and Clinician's Global Impression Scale). Benefits were greatest with the 5 mg/day dose. Hence, in PD patients with depression and motor dysfunction, consideration should be given to the introduction of pramipexole in an effort to treat both problems with a single medication.

ECT also has been used to manage depression in PD when it cannot be controlled with more traditional approaches. Benefits for both depression and parkinsonian motor features have been observed,[442,443] although the latter are typically transient and disappear in weeks to months.

Agitation. Agitation is characterized by restlessness, irritability, apprehension, and dysphoria and may be part of the spectrum of delirium or may represent an independent anxiety syndrome. Patients who become agitated during "off" periods are probably experiencing extreme anxiety rather than delirium. Their management includes better treatment of the motor fluctuations if possible. Patients who become agitated spontaneously (without provocation) or when "on" may be delirious.[444] Anxiolytics are the mainstay of treatment for primary agitation. The short-acting benzodiazepines alprazolam (Xanax), lorazepam (Ativan), and even diazepam (Valium) are most helpful. Buspirone (Buspar) also may be effective; however, it has dopamine-blocking properties that militate against its use in PD patients.

For patients whose agitation appears to be drug-related, nonparkinsonian drugs should be discontinued first if possible. Next, antiparkinsonian drugs should be discontinued in the following order of their anxiogenic potential: anticholinergics, selegiline, amantadine, and dopamine agonists. If none of the above drugs is being used or if they have been discontinued, the dose of levodopa should be reduced in an attempt to reach a balance between decreasing agitation and controlling parkinsonian motor features.

Anxiety and panic attacks. It has been estimated that approximately 40% of PD patients manifest overt anxiety, either alone or in association with de-



Breakout 12. Dietary modification, exercise, and stool softening are the first steps in treating constipation. Laxatives and enemas are reserved for refractory constipation and should not be used on a regular basis. Apomorphine injection may benefit patients with severe refractory constipation that occurs during "off" periods. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

pression.[444,445] Anxiety may be a reaction to PD or may be related to the loss of brainstem dopaminergic, noradrenergic, or serotonergic neurons. Panic attacks are characterized by a variety of psychic, autonomic, and somatic symptoms, including fear of dying, fear of going insane, breathlessness, diaphoresis, chest pain, choking, and dizziness. A panic attack may occasionally simulate a myocardial infarction.

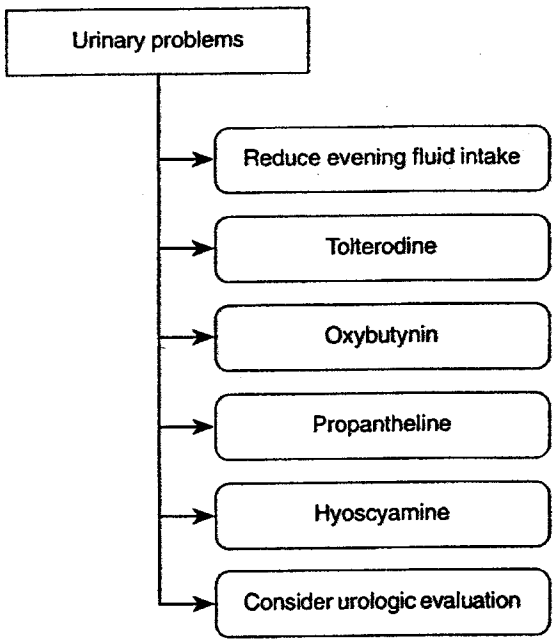
As with depression, symptoms of anxiety or panic attacks can occur exclusively during "off" periods or continuously throughout the day. Symptoms that occur predominantly during an "off" period should be managed by strategies designed to lessen the severity of the parkinsonism and to increase "on" time. If this does not sufficiently control anxiety or if the anxiety persists throughout the dosing interval, then a trial of anxiolytic drugs, such as the benzodiazepines, is warranted. The short-acting benzodiazepines alprazolam and lorazepam are preferred. A typical dose of alprazolam is 0.5 to 1 mg tid and of lorazepam is 0.5 to 2 mg tid. Cognitively impaired patients may not tolerate these agents, and a minimal dosage is suggested whenever possible.

For anxious patients or patients with panic attacks who do not benefit from benzodiazepines, an SSRI or a TCA with minimal anticholinergic activity and moderate sedative activity, such as nortriptyline, desipramine, or imipramine, can be tried. In PD patients who are cognitively impaired, these drugs can increase confusion and occasionally precipitate delirium, and must therefore be used with caution. Anxiety and panic attacks that do not respond to anxiolytics may be part of an agitated depression and may require treatment of the depression. The SSRIs are a rational choice for PD patients with both anxiety and depression. The anticholinergic and orthostatic hypotensive properties of the TCAs negate in part their usefulness for treating anxiety in parkinsonian patients.

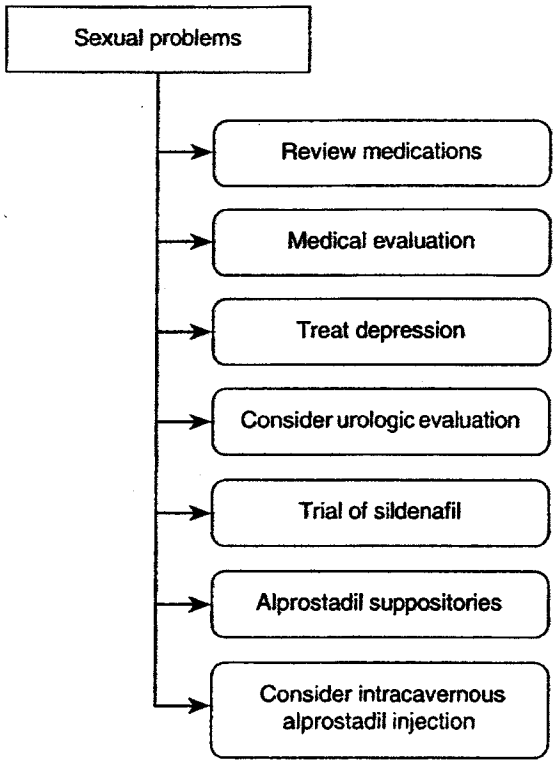
Autonomic dysfunction. Autonomic dysfunction is a common complication of PD. In fact, severe constipation and urinary incontinence were prominent features in the patients originally described by James Parkinson in 1817.[1] For most patients, dysautonomias are mild and are overshadowed by the more prominent motor dysfunction. However, a significant minority of parkinsonian patients experience very severe and disabling autonomic impairment. Autonomic disturbances in PD can manifest as constipation, urinary problems, incontinence, impotence, orthostatic hypotension, impaired thermoregulation, pain, sensory disturbances, and dysphagia.

Constipation. Two distinct processes are responsible for normal defecation. First, muscles in the intestinal wall contract sequentially to move stools through the colon. Second, there is coordinated contraction of the muscles of the rectum, pelvic floor, abdominal wall, and diaphragm, combined with relaxation of the muscles of the anal sphincter. Colon muscle activity is regulated by intrinsic enteric neurons together with extrinsic parasympathetic afferent and efferent fibers that mediate excitatory and inhibitory innervation to the colon.[446-448] There is evidence that these neurons are affected in the PD process based on the presence of Lewy bodies in degenerating neurons in the myenteric plexus of the colon of PD patients.

The primary clinical correlate of constipation is slowed stool transit time related to impaired colon muscle contraction. Impaired defecation also may relate to a primary defect in innervation of local musculature. Parkinsonian patients may be unable to straighten the anorectal angle on straining, thereby accentuating its flap valve action and obstructing the passage of stool. It has been suggested that this paradoxical contraction of the pelvic musculature is dystonic in nature and correlates with the progression of PD. In support of this argument, apomorphine can alleviate this defecatory problem in some patients with PD.[449] Other disorders that can be associated with constipation in PD patients include megacolon and sigmoid volvulus.



Breakout 13. Detrusor hyperactivity is the most common cause of urinary frequency, urgency, and nocturia in PD patients. However, because the cause dictates the choice of treatment, a urologic consultation should be considered if patients do not respond to initial therapy. Limiting evening fluid intake is the first step in treatment. If this fails, a course of tolterodine, oxybutynin, propantheline, or hyoscyamine is an additional option. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*



Breakout 14. The management of impotence in men with PD includes identification of causative drugs and/or underlying medical conditions. Many patients may be clinically depressed and should be treated with antidepressants. For patients in whom a medical or psychiatric source is not found or in whom treatment is suboptimal, a urologic consultation should be obtained and local vasodilator therapy considered. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

The management of constipation in PD consists of dietary changes, exercise, and pharmacotherapy (breakout 12). Dietary modification is aimed primarily at increasing the bulk and softening the stool. This should be the first treatment strategy and is efficacious in most patients. Patients should be encouraged to drink at least eight glasses of water each day and to increase the fiber content of their diet. Low-fiber foods such as baked goods should be eaten infrequently, and bananas should be avoided altogether. At least two meals per day should include high-fiber raw vegetables. Oat bran can be used to add bulk and to stimulate the gastrocolic reflex while at the same time reducing the amount of protein consumed. Increasing physical activity can be helpful in managing constipation. Within the boundaries of an individual patient's physical capability, exercise should be as vigorous as possible. Walking and swimming are good exercise choices for parkinsonian patients.

If stools remain hard despite the measures outlined above, stool softeners [e.g., docusate (Colace)] given with meals or lactulose in doses of 10–20 g/day may benefit some patients. Patients should be educated about the delayed onset of effect of stool softeners and should be encouraged to continue with fluids, increased bulk, high-fiber diet, exercise, and antiparkinsonian interventions. Discontinuing medications such as anticholinergic agents may increase bowel motility, but this should be done gradually to reduce the risk for exacerbation of motor dysfunction.

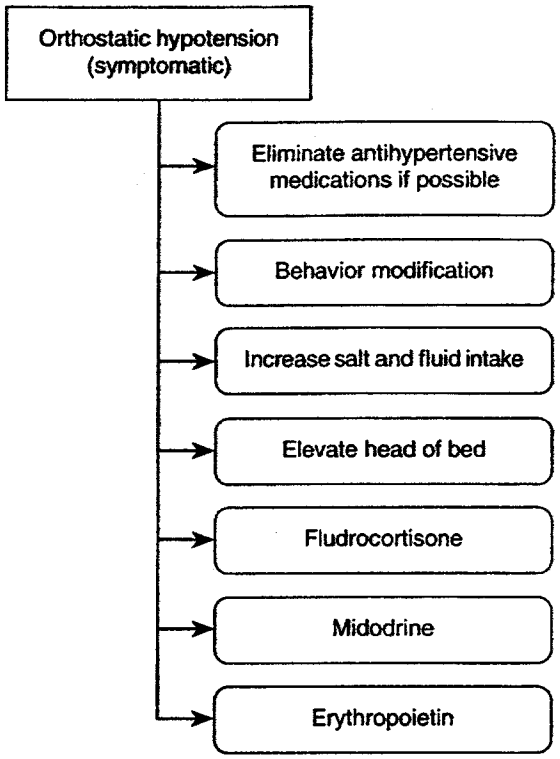
Milk of magnesia and other laxatives or enemas should be reserved until it is evident that patients have not responded to more conservative interventions, although they can be used once weekly as part of an overall bowel regimen. Apomorphine, if available, may be useful as a rescue agent for relief of severe constipation during "off" periods. Agents that promote bowel motility, such as cisapride, have previously been shown to provide benefit to some otherwise resistant PD patients,[450] but this drug has been withdrawn from the market in the United States because of reports of QT-interval changes on the electrocardiogram (ECG) and the risk for cardiac problems.

Urinary problems. Nocturia is the earliest and most common urinary problem in patients with PD. It is usually followed by symptoms of urgency and frequency as well as difficulty in micturition (breakout 13). These may be due to detrusor hyperreflexia and delayed or incomplete pelvic floor relaxation. In patients with supine hypertension, nocturia also may result from pressure natriuresis (see section on

Orthostatic Hypotension). These events correlate with the duration and severity of PD.[451] Detrusor hypoactivity or urethral sphincter dysfunction are less common causes of urinary dysfunction but may occur in PD patients with autonomic failure. If daytime frequency or urgency precedes nocturia, mechanical outlet obstruction should be ruled out. Any change or deterioration in the voiding pattern in a PD patient (even in the absence of dysuria) should raise the possibility of a urinary tract infection.[452]

PD patients with refractory or persistent urinary dysfunction should undergo a urologic evaluation. This might include recording of bladder and sphincter pressure, sphincter electromyography, and fluoroscopy. Urinary tract infection should be treated immediately. If nocturnal frequency is a problem, this may be helped by curtailing fluid intake after the evening meal. In cases in which this is not effective, peripherally acting anticholinergics can be used. Oxybutynin (5–10 mg at bedtime or tid), propantheline (7.5–15 mg at bedtime or tid), or tolterodine (Detrol) (1–2 mg bid on individual response and tolerability) can be used as initial pharmacologic treatment. If these are ineffective, hyoscyamine (Levsin, Cystospaz, Levbid, Anaspaz, Levsinex) administered at doses of 0.15–0.30 mg at bedtime or on a qid schedule can be tried. Anticholinergic agents reduce detrusor contractions and may be useful in the treatment of detrusor hyperactivity but may worsen voiding problems and even produce urinary retention in patients who have detrusor hypoactivity or outlet obstruction. Anticholinergic drugs should be administered with caution to patients with clinically significant GI obstructive disorders because of the risk for induction of gastric retention. α-Adrenergic antagonists can decrease tone in the bladder neck and may be helpful for patients with a hypoactive detrusor. However, these agents are not recommended in PD patients because they can also induce severe orthostatic hypotension. Diazepam (Valium), baclofen (Lioresal), or dantrolene (Dantrium) may be useful in relaxing striated muscle in patients with hyperreflexic external sphincters. Intermittent catheterization may be necessary if the patient has myogenic overdistension.

Sexual problems. Sexual dysfunction is a common problem in PD patients and may be the initial manifestation of autonomic dysfunction. Most attention has been focused on men, and little is known about sexual dysfunction in women with PD. In men, the most common sexual problem is in achieving or sustaining an erection. The management of male sexual dysfunction in parkinsonian patients involves identifying and correcting the underlying cause and introducing pharmacologic therapy aimed at improving erectile function (breakout 14). Previously untreated or undertreated PD patients may find that antiparkinsonian treatment helps sexual dysfunction, probably by alleviating bradykinesia and increasing desire. Some patients on high doses of antiparkinsonian therapy become hypersexual, even in the face of an inability to perform, and dose reduction may be beneficial.



Breakout 15. Evaluating antihypertensive therapy and nonpharmacologic interventions are the first steps in treating orthostatic hypotension in PD. Hypotensive therapy should be discontinued if possible. Salt and fluid intake should be increased. Patients should be instructed to elevate the head of the bed and never to lie flat. Education about the effects of eating, hot weather, bathing, exercise, and rising quickly from a prone position will assist in effective behavior modification. If pharmacotherapy is needed, fludrocortisone, midodrine, and erythropoietin (for anemia) may be helpful in normalizing blood pressure regulation. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

Many drugs can cause male sexual dysfunction, and a thorough medication history to uncover causative or contributory agents can be valuable. Propranolol and other β-adrenergic blockers, which are occasionally used to treat postural tremor or hypertension in patients with PD, should be discontinued if possible. Other drugs that can induce impotence include α-adrenergic blockers, guanethidine (Ismelin), thiazide diuretics, anxiolytics, digoxin (Lanoxin), cimetidine (Tagamet), and some antidepressants.

Medical evaluation of the impotent patient should also be performed, but it is rarely fruitful. Endocrine dysfunction can be determined by obtaining serum levels of prolactin, testosterone, luteinizing hormone, and thyroid function studies, and appropriate referral can be made if necessary. Depression is a common cause of impotence, and some antidepressants (e.g., SSRIs and TCAs) may themselves cause anorgasmia. Conversely, anxiety can be associated with

sexual dysfunction, and patients may benefit from low-dose anxiolytics.

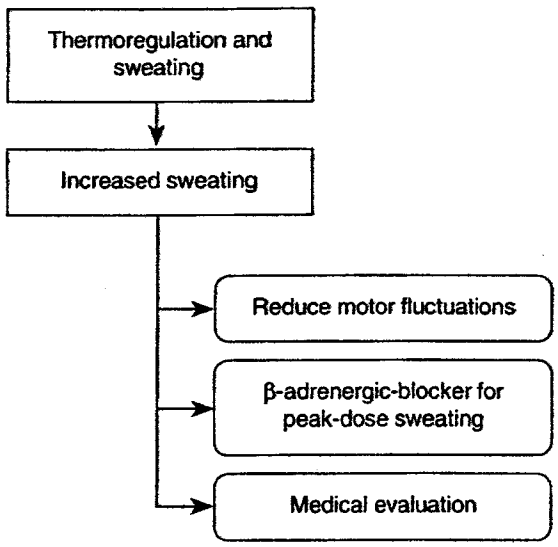
If treatment of medical and/or psychologic causes of impotence is ineffective, several therapeutic options can be considered. Sildenafil (Viagra), an orally active inhibitor of the type V cyclic guanine monophosphate (cGMP)-specific phosphodiesterase (the predominant isoenzyme in the human corpus cavernosum), is an effective treatment for impotence[453] and has been shown to be effective in PD patients as well.[454] Intracavernous injections or transurethral suppositories of alprostadil (Caverject, Edex, Muse), a synthetic prostaglandin E_1, provide a short-term vasodilator effect by relaxing smooth vascular muscle. This increases arterial inflow and decreases venous outflow by relaxing the corporal smooth muscles that occlude draining venules, thereby inducing penile erection.[455] More invasive approaches, such as implants, are available but are not readily accepted by most patients.

Orthostatic hypotension. Orthostatic hypotension in PD can be due to central or peripheral autonomic dysfunction. This is suggested by the finding of neurodegeneration and Lewy bodies in neurons involved in autonomic function in both the CNS (e.g., the hypothalamus and brainstem autonomic nuclei) and the peripheral nervous system (sympathetic ganglia, myenteric, and cardiac plexi). Maintenance of blood pressure in the standing position is a function of peripheral vascular resistance (i.e., vasoconstriction) and intravascular volume. Orthostatic hypotension in PD patients is often due to impaired vasoconstriction because of decreased sympathetic outflow. In many patients, intravascular volume is also reduced because of excessive renal sodium loss and/or anemia with decreased red blood cell mass. Excessive sodium loss can occur as a result of reduced renin release, diminished renal sodium reabsorption, or pressure natriuresis due to supine hypertension. Parkinsonian patients with autonomic failure frequently have elevated supine blood pressure and may be incorrectly diagnosed with arterial hypertension. Antihypertensives can worsen orthostatic hypotension and are contraindicated in these patients. Anemia and decreased red cell mass in parkinsonian patients may result from reduced renal secretion of erythropoietin.[456] PD patients with autonomic failure are extremely sensitive to small changes in blood volume, and even a mild reduction in plasma or red blood cell mass can markedly worsen orthostatic hypotension. Thus, orthostatic hypotension in parkinsonian patients can result both from impaired vasoconstriction and from reduced intravascular volume.

A number of effective strategies can help to avoid or treat orthostatic hypotension (breakout 15). A complete medication history should be obtained to identify and eliminate agents that can cause orthostatic hypotension, such as antihypertensive agents or diuretics. Levodopa and dopamine agonists may exacerbate orthostatic hypotension, especially during the first weeks of treatment. Gradual dosage increases when therapy is initiated or dose reductions in established patients can minimize this problem. Sodium intake should be increased in PD patients with symptomatic orthostatic hypotension. Practical methods for increasing sodium intake are the liberal use of table salt or the administration of sodium tablets. Patients should also be instructed not to lie prone at night or even during the day. Lying flat results in accelerated sodium loss from pressure natriuresis and reduced renin release, leading to loss of intravascular volume. This can lead to nocturnal hypertension with overnight volume depletion and worsening of orthostatic hypotension during the day. Elevating the head of the bed by 30–40 degrees may be helpful in preventing this phenomenon.[457] The beneficial effect of nocturnal head and torso elevation results from lessening supine hypertension, thus reducing pressure natriuresis by the kidney and, in some patients, by increasing renin secretion.[458]

Patients and their families should be educated about the hypotensive effects of food, hot weather, and physical exertion. In patients with autonomic failure, eating can significantly lower blood pressure because the splanchnic vasodilatation induced by food is not compensated for by vasoconstriction in other vascular beds. In some patients, hypotension occurs only postprandially. Therefore, PD patients should eat frequent small meals with low carbohydrate content and avoid alcoholic beverages. Caffeine taken with breakfast may be helpful. Hot baths also can induce hypotension and should be avoided. Patients should be especially careful during warm weather. This is because heat-induced vasodilatation still occurs in these situations, but sympathetic vasoconstriction is impaired. Straining at stool with a closed glottis (i.e., producing a Valsalva maneuver), playing wind instruments, and singing can be dangerous for PD patients with hypotension. A high-fiber diet is encouraged to prevent constipation, and singing or playing wind instruments should be undertaken only when sitting. Exercise is encouraged, but it should be noted that isotonic exercise produces less hypotension than isometric exercise, and exercise in a pool prevents blood pressure reductions. The use of knee-high compressive stockings is not effective in treating orthostatic hypotension, but waist-high stockings (e.g., Jobst stockings) or abdominal binders may be an effective countermeasure for orthostatic hypotension, although these are usually poorly tolerated by the patient.

Orthostatic hypotension should be treated only pharmacologically in patients who are symptomatic. Because of adaptive cerebral autoregulatory changes, patients with autonomic failure frequently tolerate very low arterial pressures when standing without experiencing symptoms of cerebral hypoperfusion. Blood pressure levels change throughout the day and from one day to another. Therefore, the patient's normal cycle of blood pressure and orthostatic symptoms should be identified before treatment is initiated. The physiologic underpinnings of ortho-



Breakout 16. Excessive sweating may occur during "off" periods and may respond to increased dopaminergic therapy. Patients also may experience sweating in association with peak-dose chorea. Here, a dose reduction or a β-adrenergic blocker may improve symptoms. Finally, a medical evaluation may uncover an endocrine dysfunction or other medical cause of impaired thermoregulation. Reproduced with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

static hypotension in PD guide its pharmacologic management (see breakout 15), which consists of strategies aimed at increasing intravascular volume, increasing peripheral vascular resistance, and correcting anemia if present. Fludrocortisone (Florinef) is a salt-retaining steroid that is widely used to increase intravascular volume in PD patients with symptomatic orthostatic hypotension. Therapy with fludrocortisone typically is initiated at a dose of 0.1 mg per day. The daily dose can be increased, but generally to no more than 0.5 mg per day. Maximal clinical response occurs after approximately 1 week; dosage adjustments should take into consideration this delayed onset of effect. Pedal edema and weight gain of 5–7 pounds are expected consequences of fludrocortisone therapy.

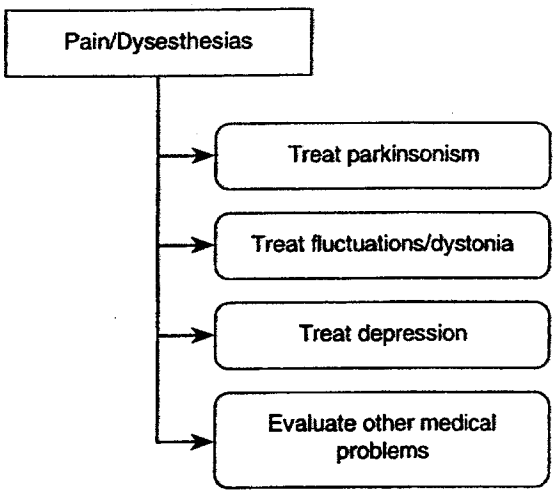
Desmopressin (DDAVP, Stimate) is a possible adjuvant to fludrocortisone therapy. It is a synthetic vasopressin analogue that acts on the V_2 receptors of renal tubule cells to reabsorb water and expand intravascular volume. It is administered intranasally in doses of 5 to 40 μg at bedtime. DDAVP can induce a severe and life-threatening hyponatremia. Therefore, careful monitoring of serum sodium concentration, preferably during a brief inpatient stay, is necessary during the first 4 or 5 days of treatment and at monthly intervals thereafter. Indomethacin, a prostaglandin inhibitor, has been used to treat orthostatic hypotension, especially in combination with fludrocortisone, but the lack of rigorous clinical data supporting the efficacy of this combination precludes a formal recommendation for its use at this time.

Sympathomimetic agents increase peripheral vascular resistance and are also useful in the treatment of symptomatic orthostatic hypotension in PD. This class of compound includes the direct-acting sympathomimetics [e.g., midodrine (ProAmatine), phenylephrine, phenylpropanolamine] and the indirect-acting agents (e.g., tyramine, ephedrine). Midodrine is a selective α_1 agonist that does not cross the blood–brain barrier and does not cause central excitatory effects.[459] The onset and offset of blood pressure response to midodrine occurs within hours of an oral dose, making this agent potentially useful in treating patients who benefit from on-demand increases in blood pressure (e.g., for postprandial and morning hypotension). Midodrine therapy is usually started at a dose of 2.5 mg and is increased to no more than 10 mg tid. A typical daily regimen includes a dose before breakfast, a dose before lunch, and a third dose in the midafternoon. Midodrine should not be administered at bedtime.

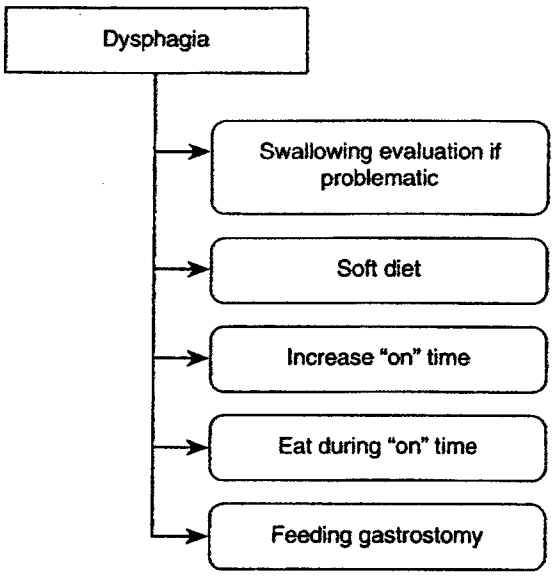
A number of investigational agents are being studied. L-threo-DOPS (the biologically active stereoisomer of the amino acid 3,4-dihydroxyphenyl serine, or DOPS) is a precursor of norepinephrine that has shown promise in the treatment of orthostatic hypotension in small clinical trials.[460,461] Further clinical studies are required to determine if this promising agent will become an important treatment of dysautonomias in patients with PD.[462] Erythropoietin (generic name epoetin alfa; brand names Epogen, Eprex, Procrit) can be used to treat orthostatic hypotension on the basis of its capacity to increase red blood cell mass and blood viscosity.[456] Erythropoietin also increases plasma endothelin, inhibits nitric oxide, and increases renal sodium reabsorption. Hypotensive parkinsonian patients with anemia may benefit from a 6-week course of subcutaneously administered recombinant erythropoietin (4,000 units twice weekly). Other treatments for orthostatic hypotension should be continued during erythropoietin therapy. Obviously, other causes of anemia in these patients should be sought and corrected if possible.

Thermoregulation and sweating. The neurochemical and anatomic bases of temperature and sweating regulation are complex and poorly understood. Preoptic and hypothalamic areas are believed to be important in thermoregulatory function. Noradrenergic, serotonergic, and cholinergic systems may also play a role in thermal homeostasis. Sweating is mediated by efferent sympathetic cholinergic fibers. Lewy bodies and cell loss have been found in the hypothalamus in PD, suggesting that hypothalamic degeneration may be involved in PD-associated sweating abnormalities.

Abnormal sensations of heat or cold, impaired sweating responses, and hypothermia can occur in the PD patient. Excessive sweating of the head and neck may occur in response to external heat and is associated with poor heat dissipation. Some of these phenomena disappear with levodopa treatment.[463] Severe drenching sweats can occur as an end-of-dose "off" phenomenon in patients with motor fluctua-



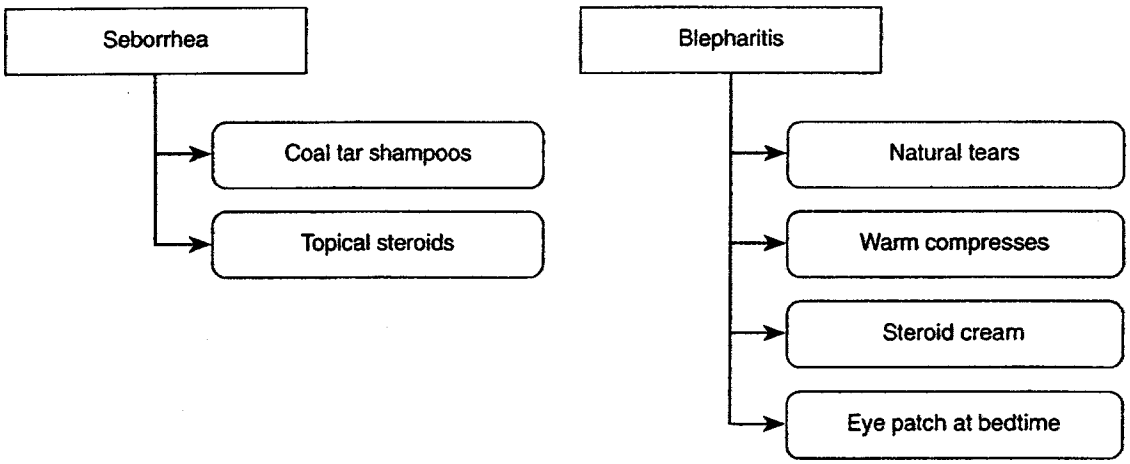
Breakout 17. Optimizing antiparkinsonian medications can reduce pain related to PD. Other causes for pain should be evaluated and treated as appropriate. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*



Breakout 18. Patients with significant difficulty in swallowing should be seen by a speech/swallowing expert. A soft diet may help. Dysphagia is usually less severe during "on" times, and efforts should be made to increase "on" time with additional dopaminergic medication. These patients should only eat during "on" times. Invasive interventions, such as a feeding gastrostomy, are a last resort. Reproduced with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

tions. Dopaminergic agents may be of benefit to such patients (breakout 16). In contrast, some patients can experience sweating during "on" responses after levodopa administration, often in association with dyskinesia. Although sweating in the "on" state can be pronounced, it is rarely as severe as that seen in the "off" state. A reduction in dopaminergic medications may help these patients but often at the price of more "off" time. Patients with "on"-period sweating are more likely to respond to β-adrenergic blockers than are patients with "off"-period sweating. Severe hyperpyrexia after levodopa withdrawal can represent a form of neuroleptic malignant syndrome and should be promptly treated by reinstitution of dopaminergic agents.

These findings support a role for central dopamine systems in thermoregulation and the regulation of vasomotor tone, although the mechanisms are poorly understood. Other causes of excessive sweating must not be neglected simply because the patient has PD. Benign sweating can occur with visual, olfactory, or gustatory stimuli. Ethanol and aspirin in high doses can cause intermittent sweating. Thyrotoxicosis and the postmenopausal state should be considered and appropriate endocrine evaluation and treatment initiated if appropriate. Finally, chronic infections, such as tuberculosis, should be considered in the differential diagnosis. A thorough history and physical examination will usually clarify these situations.



Breakout 19. Coal tar shampoos can be used for seborrhea over the eyebrows and forehead. Topical hydrocortisone (used daily) and topical ketoconazole are other treatment options. Blepharitis should be treated with natural tears and warm compresses. Steroid creams and eye patches are occasionally warranted. Reproduced with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

Pain/dysesthesias. Pain can occur in up to 50% of parkinsonian patients and is typically nonspecific. The mechanism responsible for pain in PD is unclear and is probably not the same in all patients. It can be mediated via peripheral, somatic, and central or peripheral autonomic nerves. Pain syndromes may be associated with dystonia, suggesting that PD-associated pain may arise from abnormal firing in afferent nerve fibers within dystonic muscles. A spinal cord or cerebral origin for some pain syndromes is suggested by a pseudoradicular or thalamic pattern of distribution. Many pain syndromes occur only in the "off" state, suggesting a role for dopamine-containing cells in the diencephalon, which terminate on receptors in the dorsal horn and the intermediolateral column of the spinal cord.[464-466]

Sensory symptoms are often neuritic in character and may include paresthesias, burning dysesthesias, coldness, numbness, and deep aching within a nerve or root distribution.[467] The legs are more often involved than the arms, with the face and neck being less commonly affected.[468] Akathisia also may be present. Pain is often, but not always, more severe on the side of the body where the parkinsonian symptoms are the worst.[469]

Pain related to parkinsonism often responds to adjustment of antiparkinsonian medications (breakout 17). Often it is linked to "off" states or insufficient doses of dopaminergic therapy. Therefore, optimizing medications can be helpful. Causes of radicular pain and neuropathy must be evaluated and treated as appropriate. Pain related to arthritis is not uncommon in elderly patients with PD.[470] In fact, arthritic pain or bursitis in the shoulder or dystonic pain in the foot are often early and even presenting features of PD. They usually respond to the introduction of dopaminergic therapy, particularly dopamine agonists.

Dysphagia. Dysphagia in patients with PD is usually but not always related to disease severity and eventually occurs in up to 40% of patients.[471,472] Direct involvement of oropharyngeal muscles is suggested by the observation that many patients suffer severe dysphagia only when "off," a situation that improves dramatically as soon as a dose of levodopa becomes effective. Swallowing abnormalities may be due to abnormal lingual control and inability to pass a bolus of food backward into the pharynx. Silent aspiration with repetitive reflux of food from the vallecula and pyriform sinuses into the oral cavity can be a significant and potentially dangerous problem. Excessive drooling due to swallowing abnormalities may be annoying and can cause local erosion of skin. Retention of food and pills in the vallecula is a potential cause of erratic levodopa absorption and therefore is a secondary cause of dysphagia. Esophageal dysmotility occurs in as many as 70% of PD patients, but this is a common problem in controls as well.

PD patients who experience clinically significant swallowing dysfunction should be evaluated by a speech and swallowing expert (breakout 18). Swallowing studies may help to define the nature of the dysphagia and the presence or absence of silent aspiration. Soft diets help most types of dysphagia by making it easier to move food in the mouth and esophagus. Soft food also decreases aspiration by reducing the need for separate fluid intake, which is a potential source of aspiration. Because dysphagia usually is worse during "off" time and improved in "on" time, the best strategy is to increase "on" periods by adjusting dopaminergic therapy if possible. Patients should be instructed to eat only during "on" times. Feeding gastrostomies or jejunostomies are a last resort and are only rarely necessary for patients with idiopathic PD. However, these procedures can provide the benefit of allowing more normal food and medication intake.

Seborrhea/blepharitis. Excessive secretion of oil by sebaceous glands with seborrhea of the head, face, and neck is common in PD. Blepharitis is a related problem that can be aggravated by decreased blinking and is also common in parkinsonian patients.

Coal tar shampoos can be used as a treatment for dandruff and for the seborrhea that develops over the eyebrows and forehead (breakout 19). Their use should be restricted to no more than twice weekly. Selenium-based shampoos also may work in some patients when used in a similar manner. Topical hydrocortisone is most effective on the face but must be applied daily. Topical ketoconazole is an alternative treatment for seborrhea in PD.

Blepharitis is a common problem in PD and can potentially lead to a keratitis. In most instances it is related to a combination of seborrhea and decreased blinking. Initial treatment consists of the use of natural tears and warm compresses applied three to four times per day. In more severe cases, steroid creams can be effective. If blinking is severely impaired, eye patches may be necessary at bedtime to avoid corneal abrasions from local trauma.

Falls. Falls are a leading cause of morbidity and mortality in the elderly population and frequently contribute to the need for nursing home placement.[473,474] Parkinsonism routinely emerges as a major risk factor for falls in surveys of the elderly.[474-476] Indeed, falls are extremely common in patients with advanced PD.[477-479] Risk factors include older age, longer duration of disease, advanced stage of disease, rigidity, bradykinesia, inability to rise from a chair, posture and gait impairment, postural instability, and levodopa-induced dyskinesia.[479-482] Other factors can include mental status changes, orthostatic hypotension, and vestibular dysfunction. In general, falls in PD patients are related to (a) postural instability, (b) freezing and festination, (c) levodopa-induced dyskinesia, (d) symptomatic orthostatic hypotension, (e) coexistent neurologic disorders, (f) other medical disorders, and (g) local environmental factors. Falls are more likely to occur in patients with atypical parkinsonisms, such as MSA and PSP, and these diagnoses should be considered when falls are a

prominent feature, particularly early in the course of the illness.

The clinician confronted with a parkinsonian patient who is falling should not assume that the cause of all falls is the same. Because falls or their basis may not be readily detected on physical examination, the clinician must take a careful history to determine the true frequency of falling and the potential causes and contributing factors. Identification of the probable cause is important for developing an effective treatment plan. Factors that contribute to falling in PD patients are discussed below.

Postural instability. Impaired postural responses are most likely to cause a fall when the patient changes position (e.g., when turning, getting out of a chair, or bending over). The physical exam correlate is an abnormal "pull test," in which the patient takes an extra number of steps or cannot maintain balance when pulled backward. The examiner should be sure to be in a position to catch the patient when the pull test is employed to prevent a fall to the ground and possible injury. Occasionally, patients may experience toppling falls, characterized as falling like a log from a standing position with no apparent cause. Toppling falls tend to occur in advanced PD patients with marked gait and balance impairment. Should toppling falls occur early in the course of PD or in patients with other neurologic signs, other causes, such as PSP, MSA, or a multi-infarct state, should be considered.

Postural instability related to parkinsonism may respond to drug therapy early in the disease. However, patients with more advanced PD typically fail to improve with levodopa or other dopaminergic agents. Pallidotomy and DBS of STN or GPi have a variable effect on postural response. Some patients may show benefit, but this is usually not greater than can be attained with levodopa. Physical therapy, gait training, and home safety assessment may be beneficial, particularly in making the patient and family aware of the postural instability and how it might lead to falls. Patients can be trained to consciously center their feet under their body and thus to provide themselves with a more stable platform and thereby minimize the risk for a fall, particularly when arising from a chair. Similarly, they can be taught to turn in an arc rather than pivoting in one place. In patients with more severe postural instability, walkers can be used to provide additional support. Eventually patients may become so incapacitated that they require assistance to avoid falling and may be effectively confined to bed or to a wheelchair.

Freezing and festination. Freezing refers to a patient's feet "sticking" to the ground while walking. Freezing episodes are transient, lasting for a few seconds to a few minutes, and may occur in either "on" or "off" periods. Freezing is most likely to occur when the patient initiates walking (start-hesitation), turns (turn-hesitation), passes through a doorway, or becomes distracted. In contrast to freezing, patients may festinate (run forward) because the centers of their feet lag behind their center of gravity, causing them to have to run forward and thereby putting themselves at risk for falling. As the patient walks, the flexed trunk precedes the lower limbs, leading the patient to take increasingly fast but short steps that often end in a fall.

Pharmacologic treatment of freezing is usually ineffective, particularly in more advanced stages of the disease.[483] Occasionally, manipulation of levodopa dosages or adding or taking away a dopamine agonist may help and is worth a try.[484,485] Mechanical aids, such as a walker, a tripod cane, or eventually a wheelchair, may be necessary. Motor and sensory tricks may help patients deal with freezing episodes. These include voluntary efforts to alter the distribution of body weight, walking sideways, performing rocking movements of the body, stamping the feet, walking briskly, and taking long steps.[486] Having someone rhythmically pull, rotate the trunk, rock the trunk from side to side, or passively elevate the patient's knee also may help, but care must be taken to avoid inducing a fall. Patients may also use verbal or auditory stimuli to help in initiating a movement when they are in the midst of a freezing spell. These stimuli can include marching like a soldier, walking to music, clapping hands, and swearing. Visual stimuli can also be used and include stepping over objects, such as the handle of a walking stick or another person's foot, the use of a specially designed cane with swing-out appendages that can be opened during freezing episodes, watching other people walk, and imagining a white line to step over. Because patients with freezing tend to fall forward on their hands and knees, knee pads, wrist guards, and helmets may prevent injury (review subsection on Freezing in section on Management of Motor Complications; see also breakout 6).

Levodopa-induced dyskinesia. Levodopa-induced dyskinesia is a relatively uncommon cause of falling and, as a rule, patients do better in "on" than in "off" states. However, occasionally dyskinesia may be so severe as to cause a patient to fall to the ground. Treatment is aimed at attempts to better control dyskinesia (see above). Still, in advanced stages, it may not be possible to induce periods of good mobility without complicating dyskinesia. Surgical treatments that ameliorate dyskinesia may reduce the risk for dyskinesia-related falls and in addition permit the use of higher doses of levodopa to reduce the severity and duration of "off" time.

Symptomatic orthostatic hypotension. Orthostatic hypotension can cause falls in patients with PD. Because there are specific treatments for this problem (see above), it is critical to distinguish falls due to orthostatic hypotension from other causes of falling. Orthostatic hypotension as a cause of falling can be suspected when a patient reports falling on standing, often accompanied by a sensation of lightheadedness (review subsection on Orthostatic Hypotension in section on Autonomic Dysfunction; see also breakout 15).

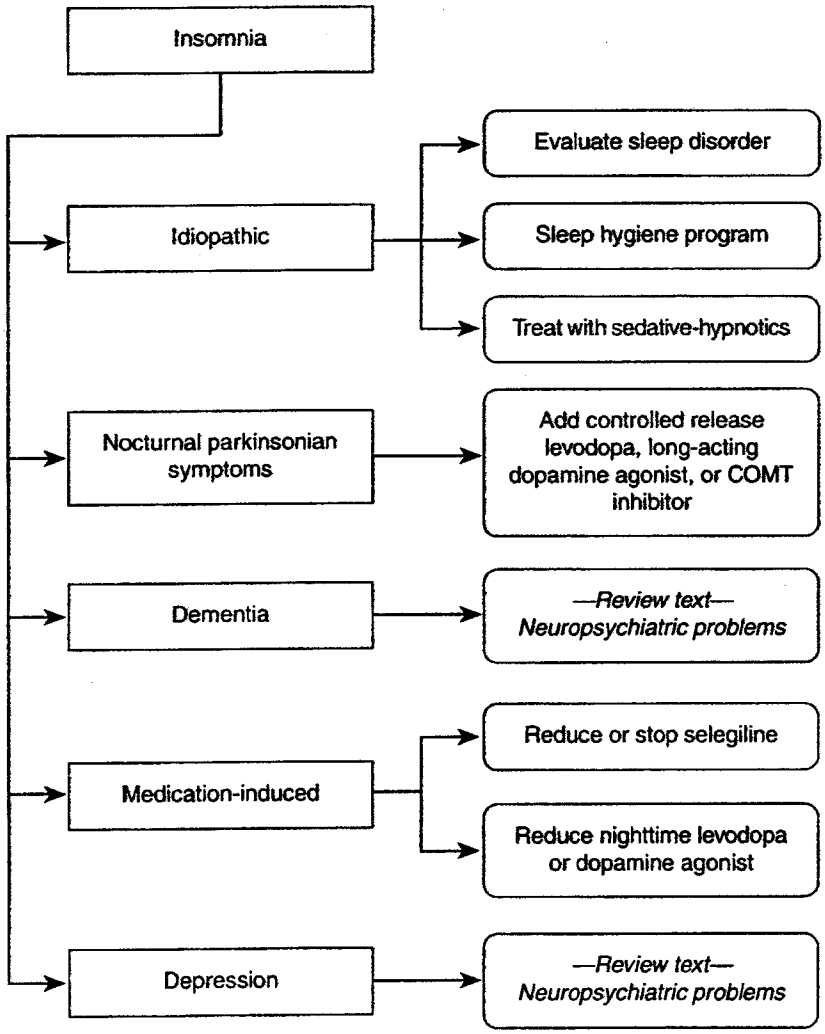
Other neurologic deficits. Nonparkinsonian neurologic deficits should also be considered as a cause of falls in patients with PD. These might include stroke, dementia, cervical or lumbar spine problems, sensory deficits (e.g., visual, vestibular, proprioceptive), cerebellar dysfunction, and generalized weakness.[474] If clinical signs and symptoms suggest another neurologic condition, an appropriate workup should be performed and treatment instituted. Muscle weakness, particularly in the legs or hips, can be associated with falling.[487] Weakness should be evaluated and, if possible, improved through the use of physical therapy and strength-promoting exercises. Clinicians may overestimate patients' muscle strength and overlook this important cause of falls.[488] Aging, arthritis, physical inactivity, and cardiac disease in the elderly also should be considered as possible contributors to muscle weakness.[489,490] Impaired vision should be considered, particularly because many vision problems are treatable. Cataracts and refractive disorders are common in the PD population, and cataract extraction or eyeglass correction may improve vision. Vestibular dysfunction, decreased proprioception, and drug effects also should be considered in the differential diagnosis of falling and should be treated if appropriate. Ataxia is an occasional cause of falls in the PD patient. Ataxia accompanying parkinsonism should raise the possibility that the patient suffers from MSA. Other causes, such as alcohol abuse and drug toxicity, should also be considered. Patients with evidence of spasticity should be evaluated for cervical spondylosis, myelopathy, and cerebral infarction. Confusion related to falls should raise the possibility of an underlying delirium or dementia. Cognitive impairment is an independent risk factor for falls in the elderly,[474] and parkinsonian patients with dementia are at particular risk for falling. Medications also can contribute to falling by causing orthostatic hypotension, fatigue, worsened neurologic deficits, or impaired mental alertness.[474] The total number of medications taken by a patient correlates with the risk for falling[491] and, accordingly, medications should be reviewed and unnecessary drugs eliminated.

Medical causes. Stable parkinsonian patients who suddenly begin to fall or have an acute increase in the frequency of falls should undergo a complete medical evaluation. Falls are a common manifestation of acute illnesses, such as pneumonia, and chronic conditions, such as congestive heart failure.[491] Arthritis can predispose to falls, particularly when the hips and knees are affected, and the risk for falling may be diminished with the use of symptomatic therapy for the arthritis. Foot problems, such as bunions, corns, or diabetes-related neuropathy, can cause patients to be unstable on their feet and fall. Such patients might benefit from referral to a podiatrist. Unexplained falls, with loss of consciousness, should raise the possibility of epilepsy or a cardiac problem. In postmenopausal women, concurrent osteoporosis may increase the risk that a patient will suffer a fracture with falling and should be addressed independently. Appropriate referral, evaluation, and treatment are important.

Environmental causes. It is important to consider environmental factors in assessing falls in PD patients. Patients may fall because they wear poorly fitting or nonsupportive footwear. Shoes with crepe or other nonskid soles, high heels, or open toes can contribute to falls in patients with a shuffling gait. A podiatrist may be helpful in recommending appropriate footwear. Patients using walkers, canes, or other ambulation devices who continue to fall should be referred to a physical therapist for evaluation of these aids because their incorrect use can increase rather than decrease the risk for falls. In addition, a trained physical or occupational therapist can make a home visit to evaluate areas for improvement in home safety (e.g., loose throw rugs, torn carpeting, slippery surfaces, small objects on the floor, poor lighting, unsafe stairways). Because the chances of falling are proportional to the number of risk factors,[474,491] everything possible should be done to correct environmental factors associated with falls.[492]

Prevention is the best strategy for managing falls in the patient with PD. The underlying cause of falling should be determined and corrected if possible. For patients with postural instability or freezing, an attempt should be made to identify the relationship of falling to the timing of dopaminergic therapy, with the treatment adjusted accordingly. In all falls, an underlying medical or neurologic condition should be sought and corrected if possible. A thorough medication history of prescription agents, over-the-counter drugs, and health food products should be obtained. Drugs can contribute to falls, particularly psychoactive drugs, hypotensive medications, and alcohol. These should be identified and either discontinued or reduced if possible. Physical therapy can improve strength, cardiovascular fitness, and balance. Educating the patient and caregiver about safe ambulation is likewise important. Trained physical or occupational therapists can provide home safety evaluations to correct environmental factors that increase the risk for falls. However, not all risk factors are correctable, and even after optimal treatment many patients continue to experience falls. The use of a wheelchair may be the best solution for these patients.

Sleep disorders. In his monograph written in 1817, James Parkinson[1] recognized that sleep disturbances are an important component of the condition he termed paralysis agitans. Sleep dysfunction is common in the elderly and is even more so in patients with PD, who are prone to have a specific set of difficulties that require proper identification and treatment.[239,240,493-500] With aging, there is disruption of normal sleep architecture as well as alterations in normal circadian rhythm, leading to daytime sleepiness and a need for daytime naps.[501] These problems are accentuated in PD patients, of whom more than



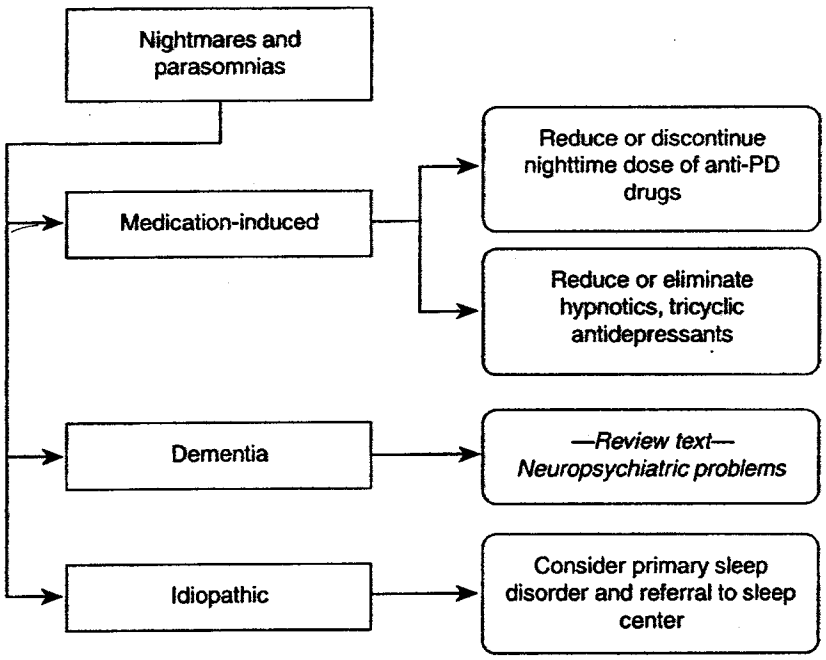
Breakout 20. Inability to fall asleep or maintain sleep is common among patients with PD. Evaluation may include all-night polysomnography or actigraphy as well as keeping of a diary for select patients. Treatment with a bedtime dose of controlled-release levodopa, a long-acting dopamine agonist, or a COMT inhibitor may be helpful if insomnia is related to parkinsonian features. Alternatively, dopaminergic medications should be reduced if the patient has insomnia because of dyskinesia. The use of sedating pharmacologic agents, particularly short-acting drugs, is an option for treating idiopathic insomnia. Small doses of TCAs may help insomnia in the depressed patient. REM behavior disorder is common and can be treated with low doses of clonazepam. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

75% have some form of sleep disturbance.[240,494,498] This usually is manifest by difficulty in initiating sleep, fragmented sleep, reversal of sleep cycle, and excess daytime sleepiness.[239,240,496,499] Sleep dysfunction in PD can be related to many factors, including aging, parkinsonian motor dysfunction, dyskinesia, pain, nocturia, nightmares, dopaminergic and nondopaminergic medications, cognitive impairment, and a variety of sleep disorders, including restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), rapid eye movement (REM) behavior disorder (RBM), and sleep apnea.[239,240,494,498,499] Collectively, these may contribute to the increase in daytime sleepiness that is frequently observed in PD patients.[500]

Sleep can be disrupted in PD patients by parkinsonian features such as akinesia, tremor, painful rigidity with stiffness, and impaired ability to turn in bed. Alternatively, dyskinesia can interfere with sleep. It is also clear that dopaminergic medications can directly interfere with sleep and, in addition, have sedative properties that may contribute to daytime sleepiness.[199,220,238-240] Therefore, dopaminergic medications can either improve or worsen sleep in PD patients. Cognitive problems also are associated with sleep disturbances and increase the likelihood of sleep problems in PD patients. Indeed, sundowning in PD patients can be more troublesome than in patients with AD.[502] Sleep disorders are particularly common in PD. Cases of RBM have been described that antedate the emergence of parkinsonian motor dysfunction,[503-505] suggesting that this condition may be an early feature of the degenerative process that occurs in PD.

The clinical importance of addressing sleep disturbances in PD has been emphasized by the recent report of eight patients who fell asleep while at the wheel of a motor vehicle.[235] These episodes were termed "sleep attacks" because they apparently occurred without warning. They were attributed to dopamine agonists because they disappeared when the drugs were withdrawn. Others have suggested that these episodes more likely represent an extreme form of excessive daytime sleepiness due to the combination of a sleep disturbance and the sedative effects of dopaminergic medications.[238]

The anatomic basis of sleep disturbances in PD is not fully understood but probably involves both the dopamine depletion that characterizes the disorder and the dopaminergic replacement therapies that

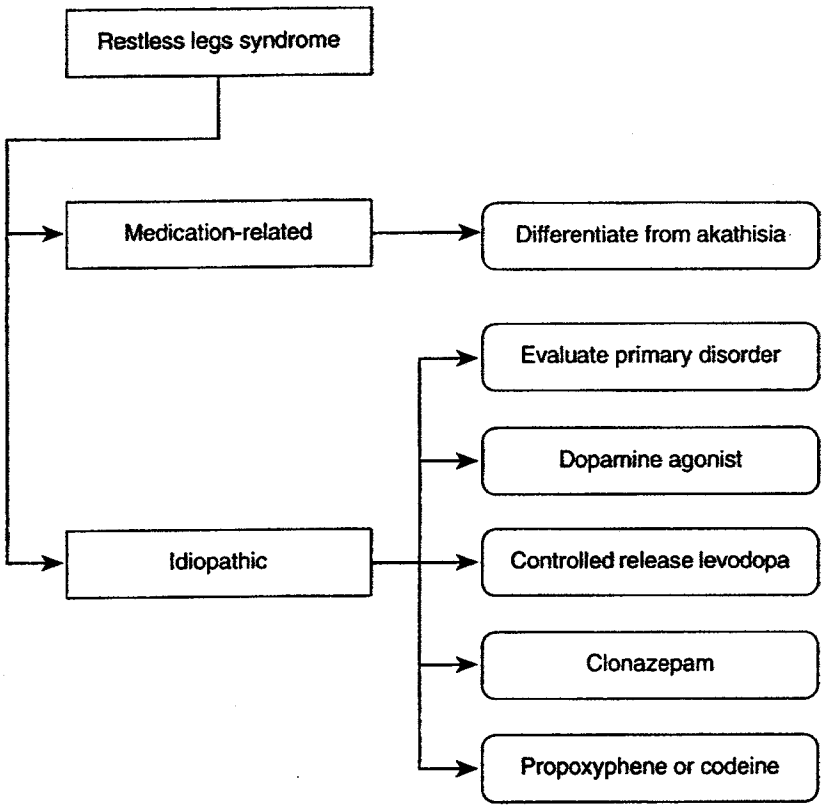


Breakout 21. Nightmares can be induced by medications, can be associated with dementia, or can be of idiopathic origin. RBD should be excluded. Dopaminergic medications frequently induce vivid dreams. Reduction in nighttime dopaminergic drugs in these cases may alleviate nightmares. Elimination or reduction of TCAs also can be beneficial. If satisfactory motor function can be obtained only with dopaminergic dosages that produce psychosis, treatment with low-dose clozapine may produce a striking benefit. An increasing number of nightmares is a harbinger of cognitive impairment and possible daytime drug-induced psychosis. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

are used in its treatment. Dopamine neurons project from the ventral tegmental area to the cerebral cortex and are thought to be involved in arousal mechanisms.[506] There is also evidence that activation of dopamine receptors can mediate sedation and sleep.[507] Dopamine agonists can produce arousal and reduced REM sleep, whereas dopamine-receptor antagonists can produce sedation and increased REM sleep.[508,509] Levodopa has been reported to both improve and disrupt sleep,[495,497,510,511] with higher doses causing higher levels of nocturnal activity and more disturbed sleep. Similarly, high doses of apomorphine have been shown to reduce REM activity and impair sleep, whereas low doses increase total nocturnal sleep time.[512] In these studies, the extent of sleep disruption has been found to correlate more closely with the dose of the dopaminergic agent employed than with disease severity. It may be that low doses of dopaminergic agents improve sleep by controlling parkinsonian dysfunction while higher doses induce adverse effects that outweigh these benefits. In this regard, it is noteworthy that the patients reported to have experienced unintended sleep episodes while driving[235] were receiving relatively high doses of dopaminergic medications (see below). It is also likely that alterations in PPN activity contribute to sleep dysfunction in PD. The PPN is intimately related to the anatomic control of sleep and probably plays a role in mediating inhibition of voluntary muscles during REM sleep.[496,513] PPN receives major inputs from the STN and GPi, and these are markedly altered in PD. In addition, neuronal cell loss and gliosis with activated microglia have been detected in the PPN in PD.[514,515] These findings suggest that degeneration and altered regulation of the PPN likely play important roles in the pathophysiology of sleep disturbances in PD.

Insomnia and sleep fragmentation. Difficulty with the initiation and maintenance of sleep may be a component of a primary sleep disorder or secondary to advancing PD, dementia, or depression (breakout 20). These all may contribute to the sleep disorder in PD, and it is important for the clinician to assess and treat each of these components. Inability to fall asleep is common among patients with PD, and a diagnosis of insomnia or fragmented sleep may be made on the basis of the patient's or caregiver's description. Sleep patterns can be further clarified with the use of a home diary or all-night polysomnography (PSG) or actigraphy.[496,498,499] In evaluating insomnia or other sleep disturbances in PD patients, it is important to obtain a careful sleep history from both the patient and the bed partner to determine how the patient sleeps and the nature of any sleep disturbance. Specifically, information should be gathered regarding the ability of the patient to turn over in bed or adjust sheets without assistance, the frequency of nocturia, and the occurrence of nightmares or other parasomnias.

In treating patients with insomnia or fragmented sleep, proper sleep hygiene can be very helpful.[516] Setting a regular time for rising and going to bed and providing bright light during the day and darkness at night can be important for setting and maintaining the circadian clock. Patients should be advised not to spend time in bed reading or watching television but should use the bedroom primarily as a place of sleep. Physical aids, such as satin sheets (for greater ease of movement) and condom catheters to deal with nocturnal urinary frequency and urgency, may be helpful. Alcohol, caffeine, and tobacco should be avoided during the latter part of the day. Reduced liquid intake before bed may reduce the frequency of nocturia. Drugs such as oxybutynin and tolterodine



Breakout 22. Restless legs syndrome (RLS) can be related to medications being taken, can be a symptom of PD itself, or can be idiopathic. If akathisia is suspected, an increase in antiparkinsonian medications is appropriate. Dopamine agonist therapy is effective for many patients. For patients taking levodopa monotherapy or combination therapy with levodopa plus a dopamine agonist, simply increasing controlled-release levodopa doses at bedtime may be beneficial. Other treatment options include low-dose clonazepam or opioids. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

may reduce bladder hyperreflexia present in the majority of PD patients, and desmopressin nasal spray may reduce the production of urine during the night.[517]

Attention should be directed at treating nocturnal PD symptoms or drug-induced motor complications. Difficulty in getting comfortable or turning in bed is often due to underdosage of dopaminergic medications or the "wearing off" of their beneficial effects. Bedtime administration of a long-acting dopaminergic preparation, such as a controlled-release formulation of levodopa, the addition of a COMT inhibitor to levodopa, or a dopamine agonist, may be useful in providing more sustained antiparkinsonian benefits during the night.[511] They also may be helpful in reducing early-morning waking because of painful dystonia. Occasionally dyskinesias can interfere with sleep. If such is the case, bedtime dopaminergic dosages should be decreased. If patients are taking selegiline, the last dose should be given no later than noon to avoid insomnia related to its amphetamine metabolites. If that is already the practice, consider eliminating the drug altogether. Amantadine also may produce insomnia because of its stimulatory effects, and dose reduction or discontinuation of the drug should be considered.

In general, long-term use of sedative hypnotics for treatment of idiopathic insomnia is not recommended because physical dependence may occur and cognitive side effects are common. If such drugs are employed, shorter-acting agents are preferred. Melatonin has been used in the form of over-the-counter preparations, but its efficacy and role in the therapy of insomnia have not been established.[518] If routine measures fail to control insomnia, the patient should be referred to a sleep specialist to rule out a sleep disorder and to consider the need for further testing with PSG.

Dementia can be associated with difficulty in maintaining nocturnal sleep and disruption of the sleep-wake cycle (see sections on Excessive Daytime Sleepiness and Unintended Sleep Episodes). Patients with insomnia should be questioned about possible depression, which can interfere with sleep[519] and, if indicated, a treatment program should be initiated. Such a program may include increased daytime activities, counseling, and the use of antidepressant medications. The soporific effects of TCAs can promote sleep onset and sleep consolidation. Typical choices include amitriptyline or nortriptyline 10 to 25 mg at bedtime. Maximal dosages are usually less than 100 mg because of the high frequency of side effects, especially in elderly patients. An alternative approach is to treat the depression with an SSRI. Although these drugs have fewer sedative properties, treatment of the depression can improve nocturnal sleep disruption (see section on Neuropsychiatric Problems).

Nightmares and parasomnias. Parasomnias, including nightmares, vivid dreams, night terrors, somnambulism, vocalizations, hallucinosis, panic attacks, and RBD, frequently complicate nighttime sleep in PD patients.[520] These can be idiopathic, secondary to medication, or associated with dementia (breakout 21). It is important to distinguish between vivid dreams or nightmares and RBD because there

Table 9 *Causes of excessive daytime sleepiness in PD*

Age-related changes in sleep architecture and alterations in circadian rhythm
PD-related disturbance in sleep–wake regulation
Disturbed nocturnal sleep as a result of
PD-related motor symptoms (akinesia/bradykinesia, tremor, rigidity)
Parasomnias with vivid dreams, nightmares, hallucinations
Sleep disorders, such as RLS, RBD, sleep apnea
Coexisting medical and psychiatric conditions, such as urinary frequency and depression
Medications that can cause sedation
Dopaminergic drugs (dopamine agonists, levodopa, selegiline)
Other antiparkinsonian agents (anticholinergics, amantadine)
Benzodiazepines, antidepressants, neuroleptics, and anxiolytics
Endocrine dysfunction, such as hypothyroidism

Table 10 *Epworth Sleepiness Scale* (reproduced with permission from Johns[241])*

THE EPWORTH SLEEPINESS SCALE

Name:_____

Today's date:_____ Your age (years):_____

Your sex (male = M; female = F):_____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze

1 = *slight* chance of dozing

2 = *moderate* chance of dozing

3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	___
Watching TV	___
Sitting, inactive in a public place (e.g., a theater or a meeting)	___
As a passenger in a car for an hour without a break	___
Lying down to rest in the afternoon when circumstances permit	___
Sitting and talking to someone	___
Sitting quietly after a lunch without alcohol	___
In a car while stopped for a few minutes in the traffic	___

Thank you for your cooperation

* Scores of >10 are consistent with excessive daytime sleepiness.

are differences in treatment. Nightmares are typically reported by patients, whereas complaints relating to RBD tend to be voiced by bed partners. Aggressive behavior or wandering during sleep suggests RBD. Dopaminergic medications may improve RBD but they often induce vivid dreams and nightmares. Patients with PD often note a return of previously absent dreaming shortly after initiation of levodopa therapy. However, it is only after several years of treatment and with the use of higher doses of levodopa that vivid dreams usually become a problem.[521] A reduction in the use of dopaminergic drugs at night can alleviate nightmares in some patients. Elimination or reduction of TCAs can also be beneficial. If optimal motor function necessitates the nighttime use of dopaminergic drugs that produce psychosis or nightmares, treatment with a low dose of a selective "atypical" neuroleptic, such as quetiapine, can be helpful (see section on Neuropsychiatric Problems). Treatment may be required only 3 or 4 nights per week.

If the bed partner reports unusual behaviors by the patient (e.g., semipurposeful actions, aggressive behavior, wandering), the possibility of RBD should be considered. In this condition there is a loss of the motor inhibition that normally accompanies REM sleep. This syndrome is most common in older men with neurologic illness, but it has been reported in a female patient with juvenile parkinsonism.[503] The violent movements that can occur in this disorder may result in injury to the patient or bed partner and can readily be misinterpreted by a bed partner who is not aware that these movements are part of the disease and not volitional. There are several descriptions of coincident RBD and PD, and a high proportion of men aged 50 years or older who present with idiopathic RBD go on to develop PD.[504,505] RBD in patients with PD can be treated with low-dose clonazepam (Klonopin) (0.25–1 mg nightly). TCAs and MAO inhibitors may precipitate or unmask RBD and should not be used.[522]

Restless legs syndrome (RLS) and periodic limb movements of sleep (PLMS). RLS is present in a high proportion of elderly individuals and PD patients, and it can contribute to nighttime sleep difficulties.[523] Clinicians should be aware of the varied manifestations of RLS, which can include uncomfortable sensations in the legs, paresthesias, aches, cramping, and an overwhelming need to move or walk. Symptoms tend to be worse in the evening or in the early nighttime, and they improve when the patient is walking, stretching, or exercising. RLS can be idiopathic, a symptom of PD, related to medication, or associated with many other conditions, such as neuropathy. A diary recording the timing of medication and the presence or absence of nocturnal symptoms may help clarify a relationship to medication. Dopaminergic agents are the treatment of choice for RLS in PD patients (breakout 22). Both levodopa and dopamine agonists can be effective, but dopamine agonists are usually favored because of their relatively long half-life and the reduced risk for

a rebound effect the next day.[524-526] Doses required to treat RLS tend to be low. If patients are receiving only levodopa, a controlled-release formulation can be used at bedtime or a COMT inhibitor, such as entacapone, can be added to the nighttime dose. The cause of RLS is not known, but dopaminergic systems have been implicated because of the response to dopaminergic medications.[527] RLS is distinct from akathisia, which is also common in PD[528] and is most often related to underdosage or "wearing off" of the levodopa effect.[529] If akathisia is suspected, adjustment of antiparkinsonian medications or treatment with clozapine may be helpful.[530] It is unclear whether PD-related leg restlessness is identical to idiopathic RLS; still, in most instances, both respond to dopaminergic therapy.

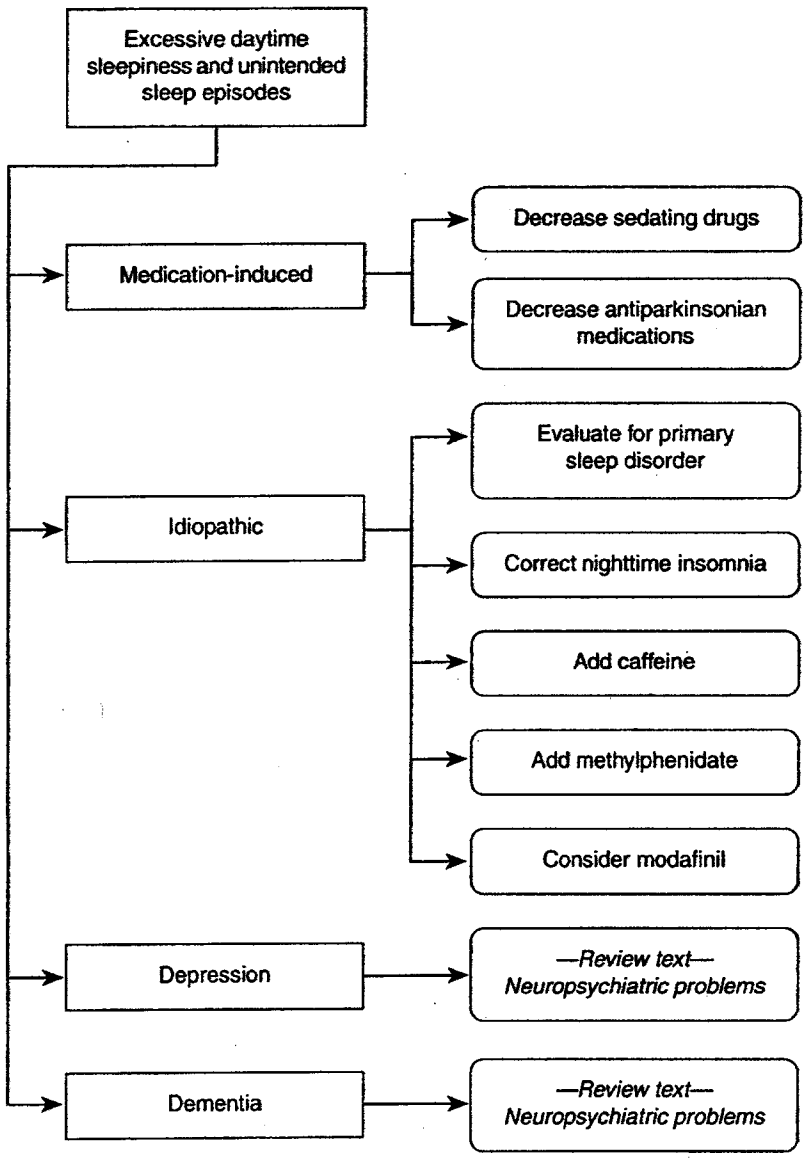
PLMS can also interfere with nighttime sleep. Approximately 50% of patients with RLS have associated PLMS.[523] Termed "nocturnal myoclonus" in the past, this syndrome may be so mild that it can be detected only with PSG or so severe that it forces the bed partner to sleep in a separate room. The movements resemble fragments of the triple flexion or Babinski reflex. They last 0.5 to 6 seconds and occur every 20 to 40 seconds. These movements can profoundly disrupt normal sleep architecture, leading to insomnia and excessive daytime sleepiness. They tend to respond dramatically to levodopa and dopamine agonists,[524] implying that they are in some way related to reduced dopamine activity in the brain or spinal cord. However, the specific neuronal systems that are responsible for these movements have yet to be determined.[531] Nevertheless, it is clear that symptoms worsen with insufficient dopaminergic treatment and are relieved with increased medication. As noted above, long-acting dopaminergic treatments, such as dopamine agonists and/or controlled-release formulations of levodopa with a COMT inhibitor, are most effective. In the occasional patient in whom RLS symptoms persist, other treatment options can include low-dose clonazepam or opiates (e.g., codeine 30 to 60 mg nightly). TCAs may exacerbate RLS and PLMS and should be avoided.

Excessive daytime sleepiness and unintended sleep episodes. Because of the many potential problems that can interfere with nocturnal sleep in PD patients and because of the tendency of dopaminergic medications to induce sedative side effects, excessive daytime sleepiness is a common problem in PD (table 9). PSG recordings indicate that the average PD patient obtains only 4 or 5 hours of documented sleep per night instead of the approximately 8 hours that are normally required.[520,532] As a result of these factors, PD patients commonly experience excessive daytime sleepiness. In a survey of 100 consecutively presenting PD patients, more than 50% had excessive daytime sleepiness based on history alone, which tends to underestimate the true frequency of sleepiness (see below).[533] Patients with excessive daytime sleepiness have a tendency to fall asleep in unintended situations. Typically, these occur in relatively benign situations that are conducive to falling asleep, such as while watching TV, listening to a lecture, or reading quietly. However, in extreme situations patients may fall asleep during a meal, while in conversation, and in potentially dangerous situations, such as when driving a motor vehicle or operating heavy machinery. The problem is complicated by the fact that many patients are not aware that they are sleepy before falling asleep because of the amnestic effects of sleep and the fact that they have become tolerant to the sensation of chronic sleepiness. To identify sleepiness in an individual patient, it may be necessary to utilize sleep questionnaires, such as the Epworth Sleepiness Scale (ESS),[241] which do not rely on subjective estimates of sleepiness but rather on a measure of the propensity of the patient to fall asleep (table 10).[241] The ESS has been shown to correlate with more expensive and time-consuming tests, such as the Multiple Sleep Latency Test (MSLT), in patients with sleep apnea and is now being evaluated in PD. Factors that can contribute to excessive daytime sleepiness in PD patients are shown in table 9.

Table 11 *Management options for excessive daytime sleepiness and unintended sleep episodes[238, 242]*

Ensure correct diagnosis: rule out syncope, seizures, cardiac disorder
Assess with validated sleepiness scale (e.g., Epworth)
Counsel patients on risks for potential daytime drowsiness and possibility of falling asleep
Consider need for polysomnography and possibility of sleep disorder (e.g., sleep apnea, RLS) and treat when appropriate
Teach patients how to improve sleep hygiene
Improve management of parkinsonian motor symptoms with dopaminergic agents
Reduce, eliminate, or reschedule concomitant sedating medications (e.g., benzodiazepines, antidepressants) or medications that interfere with drug metabolism (e.g., cimetidine)
Use lowest dose of dopaminergic agent that provides satisfactory clinical response
Reduce dosage of dopaminergic agent if patient has evidence of excessive daytime sleepiness
Evaluate for possible contributing medical conditions (e.g., hypothyroidism)
Evaluate for depression and treat accordingly

The clinical importance of sleep disturbances in PD patients is highlighted by the recent report of "sleep attacks" in PD patients.[235] The authors used the term sleep attacks because sleep apparently began suddenly and without warning. These attacks were attributed to the use of the dopamine agonists pramipexole and ropinirole because the incidents stopped when the drugs were discontinued. This report has generated intense interest in the nature and frequency of sleep disturbances in PD and has also generated a debate as to whether these episodes are unique to the use of dopamine agonists, a non-

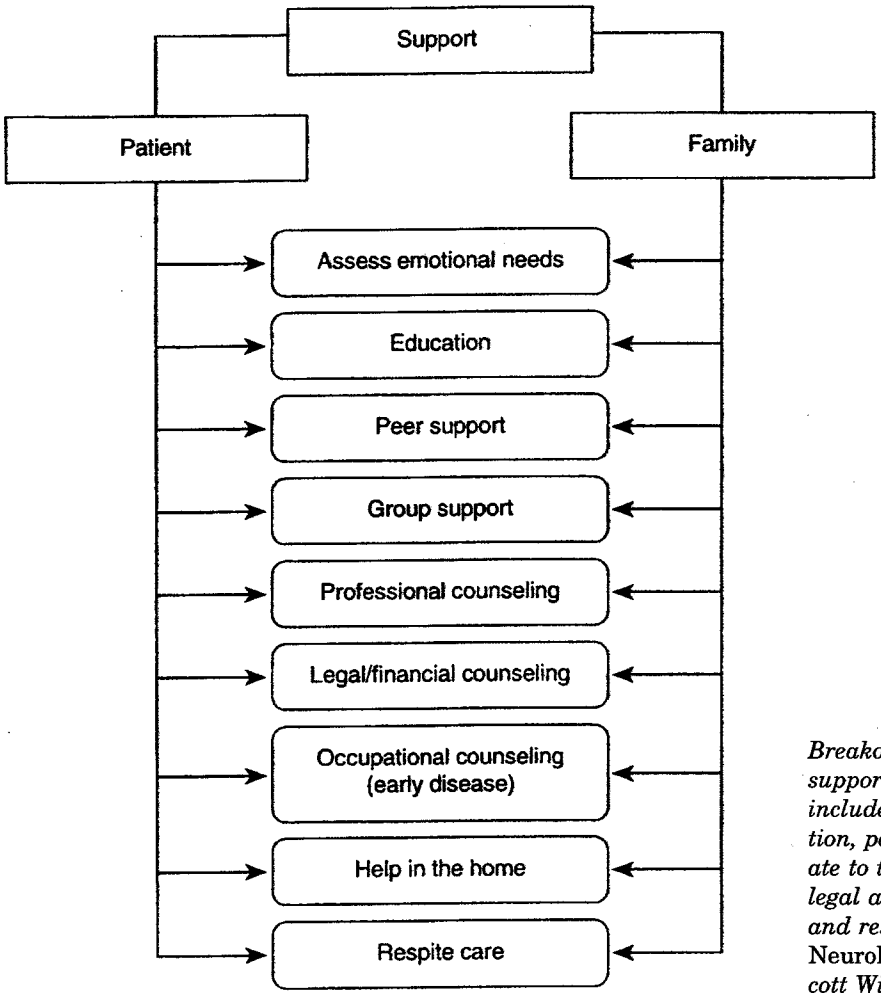


Breakout 23. Many factors contribute to excessive daytime sleepiness and unintended sleep episodes. Daytime use of sedating medications should be minimized. If untreated depression exists, treatment with an alerting antidepressant or low bedtime doses of a TCA or trazodone may help to alleviate daytime sleepiness. Primary sleep disorders or medical conditions such as hypothyroidism should be addressed and treated if appropriate. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

specific phenomenon that represents an extreme form of somnolence, or an event that is relatively specific to PD.[235-238,534] Sudden-onset REM sleep, which may occur with hallucinations, has been described in PD patients, raising the possibility that alterations in neural mechanisms in PD may contribute to sleep episodes in PD patients.[499,534] Sleep attacks in which patients fall asleep without an antecedent warning of sleepiness are not known to occur either physiologically or in association with pathologic conditions.[238,239] For this reason, the concept of a sleep attack has been abandoned even in narcolepsy and is not included among the classification of sleep abnormalities recognized by the American Sleep Disorder Association.[535] Rather, it has been proposed that the reported sleep attacks represent an extreme form of sedation in patients who are sleep-deprived and receiving sedative medications, and that this phenomenon would be better termed "unintended sleep episodes." The concept of a sleep attack implies that the events are inevitable and occur without any warning whatsoever. The notion of unintended sleep episodes implies that at-risk individuals can be identified and the episodes prevented by instituting appropriate treatment measures.[242]

Although the so-called sleep attacks were initially described in patients receiving pramipexole and ropinirole, it is now clear that sedative effects and unintended sleep episodes can be seen with any of the dopaminergic agents, including levodopa,[154,199,236,237,499,533] and that these effects are dose-related, occurring with greater frequency in patients taking relatively high doses of medication.[235,536] Therefore, somnolence is more likely to occur in patients taking higher doses of dopaminergic medications and is greatest at the time when a given dose reaches its maximal concentration. In fact, patients who had unintended sleep episodes while taking pramipexole were receiving larger daily doses (3.5 to 4.5 mg)[235,537] than have been described to provide maximal clinical benefit (1.5 mg).[154]

Management approaches to the treatment of excessive daytime sleepiness and unintended sleep ep-



Breakout 24. As in early PD, nonpharmacologic support for the patient with advanced disease includes assessment of emotional needs, education, peer and group support at a level appropriate to the disease stage, professional counseling, legal and financial counseling, help in the home, and respite care. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

isodes are provided in table 11[238,242] and in breakout 23. The first step is identification of at-risk patients. To accomplish this, the physician or ancillary personnel must inquire about excessive daytime sleepiness from both the patient and a caregiver, who might be better able to provide an objective assessment of the patient's sleep habits. Furthermore, patients may not recognize that they are sleepy because they have become tolerant of the sensation of chronic tiredness. As described above, the ESS[241] provides a quick and reliable assessment of sleepiness based on the propensity of the patient to fall asleep in unintended situations and does not rely on their subjective awareness of whether or not they are sleepy. Epworth scores greater than 10 are considered to be in the "sleepy" range, and such patients are at higher risk for unintended episodes of falling asleep. This should serve as a warning to the physician, who should begin to consider potential contributing factors (see table 10) and take corrective action.

Management options for excessive daytime sleepiness and unintended sudden episodes of sleep are outlined in table 11. They include introducing proper sleep hygiene, eliminating unnecessary sedative medications, using the lowest dose of dopaminergic medication that provides satisfactory clinical control, and identifying and treating sleep disorders.[242] Alerting agents, such as modafinil (Provigil), are being tested as a treatment for excessive daytime sleepiness in PD, based on anecdotal reports indicating that they may be useful in some patients. Patients with excessive daytime sleepiness should not drive a motor vehicle until this problem has been corrected. European agencies have suggested that PD patients taking dopamine agonists not drive at all, although we feel that this recommendation is too harsh and that PD patients can safely drive subject to the guidelines described above and in table 11.[238,242]

NONPHARMACOLOGIC MANAGEMENT

Nonpharmacologic interventions are fundamental elements of the overall management of PD patients. It is important for physicians, who tend to concentrate on pharmacologic and surgical approaches to the disease, also to recognize the importance of these essential aspects of care for the PD patient. They include education, support services, professional, legal, and financial counseling, management of emotional needs of the patient and the caregiver, exercise, nutrition, help in the home, and need for respite care. The needs of the patient change as the disease progresses. It has been shown that caregivers per-

form an average of 23 tasks per day on behalf of patients with stage III PD.[537] By stage IV/V of the disease, the caregivers provide an average of 30 tasks per day. This underscores the physical burden that is placed on the caregiver. In the early stages, it may only be necessary to provide educational and support services. Later, the clinician may have to evaluate the need for home healthcare and/or respite services.[537-539]

Education. On the one hand, education can provide the PD patient with an understanding of the disease and with a sense of control even as the disease continues to progress.[537] On the other hand, in the early stages of the disorder, knowledge of the potential consequences of the disease can be alarming and anxiety-provoking. At this stage, selective information is usually more helpful. Patients and families should be referred to the PD literature that is available through the national PD organizations, books written for the lay public, patient/family symposia, and information on the Internet. PD patients tend to be well educated and often bring new treatments to the attention of their physician. However, one must take care to ensure that information being disseminated over the Internet is reputable and has been scrutinized by PD authorities. Misinformation can lead to unauthorized, inappropriate, and potentially harmful treatments, diets, exercise programs, and so on. Websites associated with the major PD foundations provide an important educational resource (see below). Some books on PD include the following:

Parkinson's Disease and the Art of Moving (2000)
John Argue
New Harbinger Publications

Caring for the Parkinson Patient: A Practical Guide, 2nd ed. (1999)
J. Thomas Hutton and Raye Lynne Dippel, eds.
Prometheus Books

American College of Physicians Home Medical Guide: Parkinson's Disease (2000)
David R. Goldmann and David A. Horowitz, eds.
DK Pub Merchandise

Living with Parkinson's Disease (1997)
Kathleen R. Biziere and Matthias C. Kurth
Demos Vermande

Eat Well, Stay Well With Parkinson's Disease (1998)
Kathrynne Holden
Five Star Living, Inc.

Support. Patients and their families frequently need help in living with and adapting to a chronic, progressive illness. There are a number of useful support strategies that help patients and families cope with PD (breakout 24).

Assessment of emotional needs. Healthcare providers should routinely assess the emotional status and needs of the patient, the caregiver, and family members. Particular attention should be addressed to the coping abilities of the caregiver. Patients and family members should be questioned about the presence of depression, anxiety, stress, anger, and worry. The needs of patients and family members can be very different and should be assessed separately. Families often have the least amount of support but may themselves be desperately in need of help because of the impact of PD on their own lives. Problems can include sleep deprivation, depression, stress, financial strain, and concern about nursing home placement. A healthy and well-informed caregiver is a valuable resource for the patient with PD. A better understanding of the caregiver's needs allows more appropriate intervention on the part of the healthcare professional.[539] Emotional needs and coping strategies for patients and caregivers change as the disease progresses, and this assessment should be an ongoing process.[540]

Peer and group support. Support groups can offer psychological and social benefits to both patient and family. The value of peer support and support groups has been well established.[538,541,542] Studies have shown that interaction with others who have had similar experiences can have a positive effect on psychological well-being of patients and caregivers and can reduce the overall amount of interpersonal stress.[542,543] Practical tips on how to deal with specific problems can be invaluable. It is noteworthy that caregivers who have the largest number of backup caregivers in their support network have lower depression scores.[543,544]

Patients and families should be questioned about their support networks. If they do not know others with PD, an introduction to people with the same problems can be extremely helpful. One caveat for patients with early-stage disease is that support groups can actually have a negative impact. Seeing people with advanced stages of the disease can be frightening and depressing for the early patient. A one-on-one peer support opportunity or a support group that is designed specifically for the newly diagnosed or young-onset PD patients may be more helpful than immersion in a group of patients dealing with the consequences of late-stage disease. Information regarding local support organizations and educational materials can be obtained by contacting the following groups:

American Parkinson Disease Association, Inc.
1250 Hylan Boulevard, Suite 4B
Staten Island, NY 10305
1-800-223-2732
www.info@apdaparkinson.org

The Bachmann-Straus Dystonia and Parkinson Foundation
Mount Sinai Medical Center
1 Gustave L. Levy Place, Box 1490
New York, NY 10029
1-212-241-5614
www.dystonia-parkinsons.org

European Parkinson Disease Association
215 Vauxhall Bridge Road
London, United Kingdom SW1V 1EJ
enquiries@parkinson.org.uk

National Parkinson Foundation, Inc.
1501 NW Ninth Avenue, Bob Hope Road
Miami, FL 33136-1494
1-800-433-7022
www.parkinson.org

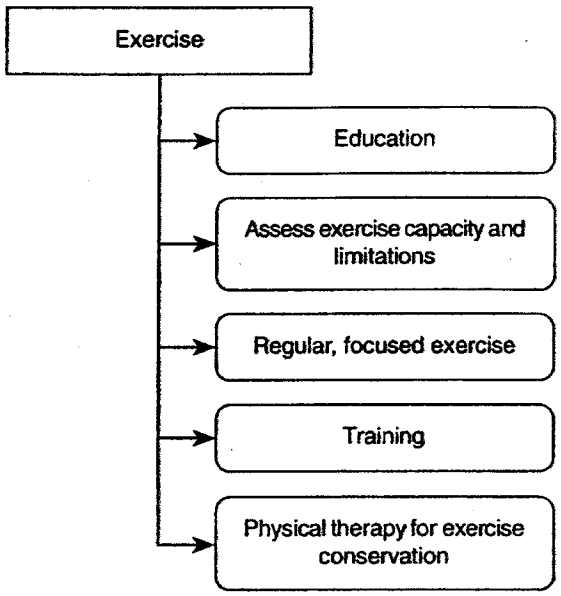
The Parkinson's Disease Foundation
710 West 158th Street
New York, NY 10032
1-800-457-6676
www.parkinsons-foundation.org

The Michael J. Fox Foundation for Parkinson's Research
840 3rd Street
Santa Rosa, CA 95404
1-707-544-1994
www.michaeljfox.org

The Parkinson Foundation of Canada
4211 Yonge Street, Suite 316
Toronto, Ontario, Canada M2P 2A9
1-416-227-9700
www.parkinson.ca

We Move
204 West 84th Street, 3rd Floor
New York, NY 10024
www.wemove.org

Professional counseling. When the stress of living with PD or living with someone who has PD becomes so challenging that coping skills begin to reach their limit, a referral should be made for psychiatric or psychological counseling. Clinicians who manage PD patients should have a list of local counselors who specialize in chronic illness so that appropriate referrals can be made. Counseling needs for spouses should be assessed separately from those of the patient. Stresses are different for the spouse, and counseling may be helpful for a spouse at a time when it may not be necessary for the patient.

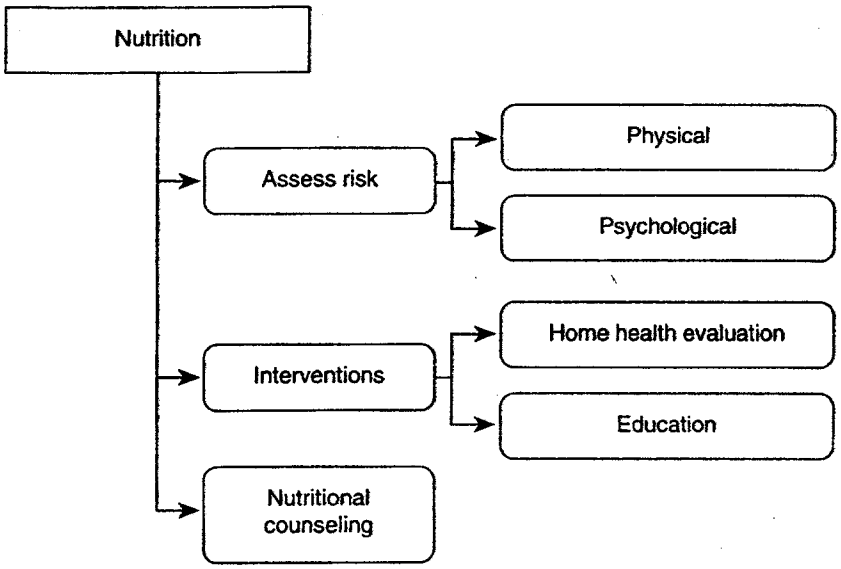


Breakout 25. Although exercise will not change the cardinal symptoms of PD, a regular, focused exercise program that includes aerobic, stretching, and strengthening activities will have positive effects on mobility and mood. A physical therapy referral to learn energy-conservation techniques may assist in dealing with the fatigue that accompanies later-stage PD. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

Legal/financial counseling. Clinicians should encourage patients to seek expert advice from attorneys or estate planners who specialize in the area of elder law and who are skilled in the financial and legal issues of chronic illness and disability. This kind of preparation by patients and their families early in the course of the disease can be very helpful in coping with some of the anxiety that comes from living with the possibility of developing increasing physical disability.

Occupational counseling. When appropriate, clinicians should inquire about performance in the workplace. Work can be an important source of self-esteem and independence, and adaptations can often be made so that the patient can maintain employment. These might include changes in job requirements, number of work hours, or workplace environment in an effort to prevent the need for premature termination or retirement.[545,546] Occupational therapists are trained to visit the workplace and consider adaptations that can be made to improve productivity and reduce stress. The ability of the patient to continue in the workplace and the need for disability insurance should also be considered.

Exercise. Exercise is an important adjunctive therapy for PD and can be beneficial for patients in all stages of the disease (breakout 25).[547] Although exercise has not been shown to directly improve the cardinal features of PD, such as bradykinesia, tremor, postural instability, and rigidity, it can pre-



Breakout 26. Nutritional assessment and intervention in the patient with advanced PD are important components of overall care. Patients should be assessed for physical and psychosocial factors that interfere with proper nutrition, including chewing and swallowing problems and inability to prepare meals. Psychosocial factors also may contribute to poor nutrition. Some may benefit from home health aids, Meals on Wheels, dietary supplements, referral to a nutritionist, and a protein redistribution diet. Adapted with permission from Neurology *Vol. 50, No. 3, March 1998. Lippincott Williams & Wilkins.*

vent the impairment in mobility or functional activity that results as a consequence of these problems.[548,549]

Patients should be educated about the positive effects of exercise on mobility and mood. An exercise program should include aerobic, strengthening, and stretching activities. One does not replace the other. Aerobic exercise should be done at a training heart rate of 60–70% of maximum. Stretching exercises should be done when muscles are warm. Strengthening exercises should be performed with light weights. The goal should be to improve flexibility and strength but not to add bulk. Emphasis should be placed on the extensor muscles to counteract the flexor postures that tend to develop in PD. A reasonable goal is a 20-minute exercise session three times a week. Patients with advanced disease also can benefit from regular focused exercise sessions. Most patients can still exercise regardless of the stage of PD. Because fatigue is an important feature of later-stage PD, it may be helpful to refer patients to physical therapy so that they can learn energy conservation techniques designed to help reserve energy for the most important activities of the day. In any instance, patients should not exercise to the point of exhaustion.

Before an exercise program is started, potentially complicating medical problems, such as heart disease, should be ruled out. The baseline level of fitness can be determined by measuring maximal heart rate. Other limitations, such as decreased range of motion in a particular joint, should be identified to minimize the risk of injury. Non-weight-bearing exercise (e.g., water aerobics) may be particularly beneficial for PD patients. Patients who are interested in an exercise program but are not sure how to get started should be referred to a physical therapist or a PD exercise group.

Nutrition. Good nutrition is essential to the well-being of PD patients. It is important to establish and maintain good eating habits throughout the course of the disease (breakout 26). Patients with PD are at increased risk for poor nutrition, weight loss, and loss of muscle mass in comparison to healthy controls.[550,551] Parkinsonian patients are four times more likely than age-matched controls to have weight loss of more than 10 pounds.[550] Conversely, obesity may become a problem because of the sedentary life-style and poor eating habits that can accompany PD. These problems can lead to generalized weakness and an increased risk for falls.

Clinicians should obtain a thorough dietary history from PD patients and define their current eating habits. Assessment of nutritional status begins with a careful history to identify patients who are losing weight and factors that might interfere with proper nutrition. These might include insufficient caloric intake, chewing or swallowing difficulties (see breakout 18), poor dentition, impaired ability to prepare meals, and the use of nontraditional diets. Energy output due to severe dyskinesias can be greater than caloric intake and can contribute to weight loss. Depression, cognitive impairment, inadequate social support, and low income are psychosocial factors that also can contribute to poor nutrition.

Helping patients become aware of their dietary habits and educating them about the elements of a balanced diet and the techniques to successfully al-

***Table 12** Future research directions*

Interventions that treat or restore function for patients with advanced disease
Interventions that treat dyskinesia
Interventions that prevent the development of motor complications
Interventions that treat "nondopaminergic" features of PD
Neuroprotective treatments

ter poor eating habits are essential. Although no specific diet is required, patients should eat a balanced diet that contains sufficient fiber and fluid to prevent constipation and enough calcium to maintain bone structure. Dietary amino acids can compete with levodopa for absorption from the GI tract and for transport into the brain. Therefore, they can cause erratic and unpredictable responses to levodopa therapy.[194,551] Patients with advanced PD should be aware of this interaction because it can lead to delayed "on" and no "on" responses if levodopa is taken with a meal, and the protein content limits the amount of levodopa that can gain entry into the brain (see breakout 4). Ideally, PD patients should take levodopa on an empty stomach to facilitate absorption, but nausea may necessitate the administration of levodopa with some food. In this case, it is preferable for patients to take levodopa with a low-protein meal. Some physicians have advocated a protein-redistribution diet in which all protein is taken with the evening meal.[299] This may be helpful for a limited period of time but it rarely provides a long-term solution to the problem. In general, this is an unpleasant and possibly improper diet, and it is better if patients can simply take levodopa on an empty stomach 1 hour before or after meals. Pharmacists may label prescriptions for levodopa with a warning to take the medication with food, but this is not desirable, particularly for patients with motor fluctuations.

A proactive approach should be taken to prevent constipation. Patients should be encouraged to increase the amount of fluid and fiber in their diets (see breakout 12).[552] Patients who have difficulty maintaining a balanced diet may be candidates for a supplemental multiple vitamin, with or without calcium supplementation. A large body of literature supports a role for oxidative stress as a contributing factor in the pathophysiology of PD.[121,553,554] However, there is currently no evidence to suggest that antioxidants (e.g., α-tocopherol or vitamin E) alter the course of the disease.[67,555] In addition, supraphysiologic or megadoses of these agents are costly and potentially dangerous. Patients occasionally may benefit from a home health evaluation to identify problems more specifically. To maintain proper nutritional status, patients may need assistance in the form of guidance aimed at improving eating habits and nutritional status, regular visits from home health aides, Meals on Wheels, or prescribed dietary supplements. However, patients should be aware that many commercially available dietary supplements are high in protein and they should become accustomed to reading labels before purchasing these products. Referral to a nutritionist for evaluation and dietary recommendations may occasionally be valuable. Patients with dietary problems due to cognitive impairment or depression should be treated appropriately (see breakouts 9 and 11, respectively).

FUTURE DIRECTIONS

It is clear that there have been important advances in our ability to manage patients in all stages of PD. Nevertheless, there remain important unmet medical needs, and even more effective therapeutic interventions are required for the successful management of the PD patient. Future research directions are presented in table 12.

Interventions that treat or restore function for patients with advanced PD. There have been considerable advances in our ability to use surgical therapies to treat patients with advanced PD who cannot be satisfactorily controlled with currently available medical therapy. Benefits in this population of patients have been reported with pallidotomy, high-frequency DBS of the STN and GPi, and transplantation procedures. None of these procedures has yet been demonstrated to provide benefits that are substantially better than can be achieved with levodopa, but they are associated with reduced motor complications so that, overall, patients experience reduced disability. Formal studies directly comparing the different surgical treatments have not yet been performed and are necessary to determine which, if any, is the superior surgical procedure. Preliminary data suggest that DBS procedures may be the best. However, these procedures still require placing a needle into the brain, the implantation of the stimulator system with associated infectious and mechanical side effects, and the periodic need to replace the battery.

Transplantation strategies are appealing because they have the capacity to restore relatively normal innervation to the striatum[129] without inducing disruption of any component of the basal ganglia system. Formal results of prospective, double-blind transplantation procedures using tissue derived from fetal human and porcine nigra are becoming available. An initial report with human fetal nigral cells indicates only modest benefit[386] and suggests that the procedure is complicated by severe dyskinesia that persists into the practically defined "off" period.[391] This study utilized a quality of life end point that had not been validated or previously used in PD. While this study was negative with respect to the primary end point it did provide some benefit with respect to more traditional outcomes. A second study utilized UPDRS motor scores as a primary end point and employed a series of transplant variable that had provided good results in open-label clinical trials. These results are anxiously awaited. Attempts to improve on results through earlier transplantation, the use of larger numbers of donors, concomitant use of lazaroids and antioxidants, and transplantation into other brain targets, such as the SNc, are being evaluated.[556,557] Stem-cell therapies have captured the imagination of many researchers because of the potential of stem cells to differentiate into the desired cell type and to have trophic qualities that direct them

to the site of neurodegeneration.[558,559] Preliminary studies indicate that stem cells can differentiate into dopamine neurons,[560] but it remains to be determined if they can both differentiate into dopaminergic neurons and retain their trophic properties. In addition, societal issues regarding the use of embryonic stem cells remain to be resolved.

Trophic factors are of great interest in PD because of their potential to rescue damaged dopaminergic neurons in both in vitro and in vivo models. GDNF has been shown to repair the damaged nigrostriatal system in animal models of parkinsonism.[98,561] A preliminary trial of intraventricular GDNF in PD patients was not successful, but this may have been because GDNF was not able to cross the ventricular barrier and gain entry into the brain.[562,563] Direct intraparenchymal injections of GDNF might be more effective. In support of this notion, gene therapy using lentivirus to deliver GDNF into the striatum and SNc of MPTP-treated monkeys has been demonstrated to restore nigrostriatal activity and motor function. Furthermore, the lentivirus was well tolerated in contrast to other viral vectors that have been utilized for gene therapies. It therefore appears that this approach is logical to test in PD patients, although there remain major concerns about the use of gene therapies in human patients. In addition, it is not certain when this type of investigation will be performed.

Interventions that treat dyskinesia. A number of drugs are being tested as possible antidyskinetic agents in PD.[564] An effective antidyskinetic treatment might permit dopaminergic agents to be administered in larger doses without fear of complicating dyskinesia and thus to provide better control of parkinsonian motor features. Such an approach also might obviate the need for surgical intervention in many patients because, for the most part, surgery is performed primarily to treat motor complications. There are no data suggesting that surgical therapies improve underlying parkinsonism to any greater extent than can be achieved with levodopa alone. It is noteworthy that levodopa continues to be effective for some parkinsonian features throughout the course of the disease and is limited primarily because of motor complications. The ability to utilize high doses of levodopa without dose-limiting dyskinesia therefore might provide substantial benefit for patients with advanced PD. The concept of continuous dopamine receptor stimulation to treat existing dyskinesia is extensively reviewed in Olanow et al.[188] and Nutt et al.[209] This can be accomplished by administering dopamine agonists through an infusion pump or levodopa via duodenal infusion.[211-213,303-306] Both types of treatment have been reported to be associated with enhanced motor responses and reduced dyskinesias. However, such treatments are cumbersome and inconvenient to administer. This approach may be valuable for an individual patient, but for the moment it is not likely to be useful for the majority of patients with advanced PD.

Other approaches now under investigation include agents that act indirectly on the dopaminergic system and include adenosine A_{2a} antagonists, opioid antagonists, 5-HT_2C antagonists, CB-1 antagonists, α_2 antagonists, atypical neuroleptics, dopamine uptake inhibitors, NMDA receptor antagonists, and selective muscarinic and nicotinic agonists.[564] Adenosine A_{2a} receptors are localized to cholinergic interneurons and cell bodies of striatal output neurons in the indirect pathway[565] and therefore can influence release of both acetylcholine and GABA. The adenosine A_{2a} antagonist KW6002 improves motor features in MPTP-treated monkeys without inducing dyskinesia,[566] and clinical trials of this agent in PD patients are under way. The NMDA receptor antagonists amantadine and dextromethorphan are associated with reduced dyskinesia in MPTP-treated monkeys, and amantadine has been reported to improve dyskinesia in PD patients.[292-295,567-569] Rimantadine is the α-methyl derivative of amantadine. It has been shown to have motor benefits in PD in an open-label study.[570] It is better tolerated than amantadine and may have a role in the treatment of dyskinesia. Riluzole, which blocks sodium channels and inhibits glutamate release, also has been reported to reduce dyskinesia in PD patients.[571] The atypical neuroleptic sarizotan has mild D_2 and D_3 receptor antagonist and potent 5-HT_{1A} receptor agonist properties.[572] The drug has been shown to markedly reduce dyskinesia without worsening parkinsonism in levodopa-treated, MPTP-treated monkeys, and it is now being assessed in clinical trials with PD patients.[573] Striatal opioid binding is reduced in dyskinetic PD patients, compatible with the presence of raised enkephalin and dynorphin levels and, indeed, [^{11}C]diprenorphine receptor binding is decreased in the striatum of PD patients with levodopa-induced dyskinesia on PET.[574] This suggests that opioid antagonists might be effective agents for the treatment of dyskinesia. In fact, small clinical trials showed that the opioid antagonist naloxone,[575,576] but not nalotrexone,[577,578] had antidyskinetic effects in levodopa-treated PD patients.

There remains interest in the potential of newer dopamine agonists to provide more effective antiparkinsonian effects with less dyskinesia. There has long been interest in the possibility that selective stimulation of dopamine D_1 and D_2 receptors might have differential effects on motor function and dyskinesia. Both D_1 and D_2 receptor agonists can induce dyskinesia in animal models of parkinsonism.[215] However, the D_1 agonists A-86929 and A-77636 have been shown to provide motor benefits with reduced dyskinesia in levodopa-primed, MPTP-treated monkeys,[579,580] and these agents are potential candidates for clinical trials in PD patients with dyskinesia.

Finally, there has been interest in treatment approaches directed at interfering with signal transduction pathways activated by nonphysiologic

pulsatile stimulation of dopamine receptors.[214] These are believed to be associated with upregulation of striatal kinases capable of phosphorylating NMDA receptor subunits, leading to altered plasticity and dyskinesia.[581,582] Indeed, inhibition of the serine kinase cAMP, protein kinase A (PKA), and tyrosine kinase calcium/calmodulin-dependent protein kinase II (CaMKII) by (Rp-cAMPS) and (KN)-93, respectively, have been shown to reverse levodopa-induced response alterations in dopamine-lesioned rodents.[583] Similarly, the tyrosine kinase inhibitor genistein reverses motor complications associated with levodopa in the rodent, whereas the tyrosine phosphatase inhibitor okadaic acid potentiates these alterations.[214] These observations support the notion that agents that interfere with signaling mechanisms that promote dyskinesia are logical candidates for testing as antidyskinetic agents in PD.

Interventions that prevent the development of motor complications. As indicated above, much of the disability that occurs in advancing PD is due to the development of motor complications. Dyskinesias can be troublesome in and of themselves but, perhaps more importantly, they limit the ability of the physician to fully utilize dopaminergic therapies and thereby provide better control of parkinsonian motor features and motor fluctuations. A treatment that prevents the development of motor complications would enhance the quality of life for PD patients, diminish the need for surgical interventions, and greatly simplify the treatment of this disorder. A great deal of attention has been directed toward this goal in recent years. Current evidence suggests that motor complications are related to the downstream consequences of pulsatile stimulation of dopamine receptors,[170] and therapy has been directed at providing more continuous dopaminergic stimulation[188] in attempts to prevent these phenomena. It is now evident that initiation of symptomatic therapy with a long-acting dopamine agonist reduces the risk for motor complications in comparison to short-acting agents such as levodopa.[153,154] Cabergoline is a particularly long-acting dopamine agonist with a half-life of more than 24 hours, which might be expected to provide relatively constant plasma levels and to be particularly valuable in this regard. However, an initial study shows benefits comparable to other dopamine agonists,[225] suggesting the possibility of a ceiling effect. N-0923 is a water-soluble dopamine agonist that can be delivered by patch[584] with minimal fluctuations in plasma concentration. This approach may be capable of providing continuous dopaminergic stimulation with a reduced risk for motor complications.

Eventually, however, all patients require levodopa therapy, which is associated with an increased risk for motor complications even when administered with a dopamine agonist. There is now interest in the notion that administration of levodopa in combination with a COMT inhibitor to increase its half-life and brain availability will reduce the risk for motor complications seen with levodopa when it is given alone. To achieve this objective, it may be preferable to administer levodopa in a controlled-release formulation. Studies to test this hypothesis are under way. Unfortunately, they are long-term studies, and it will be many years before results are available. Dopamine uptake inhibitors used from the onset of therapy might represent another way to provide stable concentrations of dopamine at the level of the receptor and to prevent motor complications.

Interventions that treat "nondopaminergic" features of PD. The development of nondopaminergic features, such as dementia, postural instability, gait disturbances, and autonomic dysfunction, is among the most disabling aspect of PD for many patients, yet we have very little in the way of effective treatment for any of these. Anticholinesterase strategies offer little to the dementia of PD patients,[421] although there are effective treatments for the psychosis that frequently accompanies PD dementia (see section on Neuropsychiatric Problems). Symptomatic treatments exist for some of the features of autonomic dysfunction, such as orthostatic hypotension, constipation, and urinary dysfunction, all of which were reviewed above, but there are no effective treatments for patients with gait dysfunction and postural instability who do not respond to levodopa. Collectively, these remain one of the major unmet medical needs in the management of PD.

Neuroprotective treatments. Laboratory clues have provided us with many rational approaches to protecting nigral neurons in PD that individually or collectively might eventually lead to a neuroprotective therapy. Clinical trials are now testing the potential benefits of dopamine agonists (ropinirole, pramipexole), antiglutamatergic agents (riluzole), bioenergetics (co-enzyme Q10), trophic factors (GDNF, neuroimmunophillins), and anti-apoptotic agents (TCH-346). Other approaches that could be considered for clinical trial as a possible neuroprotective agent include agents with bioenergetic effects (creatine, ginkgo biloba, nicotinamide, riboflavin, carnitine, and lipoic acid), antiexcitotoxic agents [NMDA, AMPA, metabotropic type I and V receptor antagonists, glutamate uptake enhancers, nitric oxide synthase (NOS) inhibitors], anti-inflammatory drugs, calcium channel antagonists, antioxidants (free radical scavengers, glutathione-enhancing agents, iron chelators), anti-apoptotic agents (caspase inhibitors, agents that promote closure of the permeability transition pore, such as cyclosporine, or agents that upregulate BCL-2, desmethylselegiline, and CEP 1347, which inhibits JNK kinase), and neuronal growth factors [including immunophillins, GDNF, fibroblast growth factor (FGF), and ciliary neurotrophic factor (CNTF)]. It will be difficult to obtain the resources to evaluate so many putative neuroprotective therapies, and an outcome measure

acceptable to neurologists and to regulatory authorities has yet to be defined.[99] However, determination that a therapy can stop the progression of PD and effect a cure is the ultimate goal.

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